

המערער:

עדן יצחק ת.ז. 208935874

ע"י ב"כ עוה"ד אריאל פרייברג ואו אחי

מרחי אבא הלל 7, רמת גן

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- נ ג ד -

המשיב:

קצין התגמולים.

ע"י ב"כ עו"ד אגסי מימון ואו עו"ד דרורי

ואו עו"ד בן ישי – גלאור ואו עו"ד מור ואו עו"ד דוד ואחי

בית קנדה, נירים 3, תל אביב 6706038

טל. 03-6200401 פקס. 03-6200406

כתב תשובה

1. כל טענות המשיב נטענות במצטבר ואו לחלופין ואו משלימות זו את זו, הכל לפי הקשר הדברים והדבקים.

2. מוכחות כל הטענות המשפטיות והעובדתיות המפורטות בכתב הערעור ובנספחיו, ובחוות הדעת מטעם המערער, למעט העובדות בהן מודה המשיב מפורשות בכתב תשובה זה.

להלן העובדות הצריכות לערעור זה:

3. המערערת, ילידת 4.3.1997, התגייסה לשירות חובה באוקטובר 2015 ושוחררה ביום 31.1.2018.

4. המערערת הגישה ביום 22.7.2021 תביעה להכרת זכות אל קצין התגמולים לפי חוק הנכים (תגמולים ושיקום), תשי"ט 1959 (להלן: "חוק הנכים") בטענה שבעיית הכליות ארעה במהלך וכתוצאה משירותה הצבאי.

5. ביום 14.10.2023 כתבה מומחית המשיב, פרופ' טליה וינשטיין, חוות דעת רפואית לאחר פגישה עם המערערה ואמה ביום 26.7.23.

מצ"ב חוות דעת מייעצת מיום 14.10.23 של פרופ' טליה ויינשטיין **כנספח 1**.

6. בהחלטתו מיום 11.2.2024 דחה המשיב את הבקשה, כי לא הוכח קשר סיבתי בין תנאי שירותה, לבין מחלת הכליות הכרונית בה לקתה כשנתיים לאחר שחרורה מצה"ל.

מצ"ב החלטת קצין תגמולים מיום 11.2.24 **כנספח 2**.

7. המעוררת הגישה ערעור על החלטה זו ואליה צירפה חוות דעת של ד"ר עודד וולובסקי מיום 26.8.2024.

8. פרופ' ויינשטיין ערכה חו"ד משלימה ביום 7.12.24 במסגרתה הגיבה לטענות ד"ר וולובסקי.

מצ"ב חוות הדעת המשלימה של פרופ' ויינשטיין מיום 7.12.24 **כנספח 3**.

טענות המשיב

9. אין כל קשר סיבתי בין תנאי שירותה הצבאי של המעוררת לבין מצב הכליות. הממצאים מצביעים על מחלה כלייתית תורשתית (TSC) אשר התפתחה ללא קשר לשירותה הצבאי.

10. לדברי המעוררת בתצהירה, היא טופלה בשתי זריקות וולטרן במהלך שירותה הצבאי **כשנתיים טרם** התייצגותה עם אי ספיקת כליות. אין כל סמיכות זמנים בין הזריקות לבין מחלתה של המעוררת. אין זה סביר כלל, לעמדת פרופ' ויינשטיין, כי AIN הופיעה לאחר תקופה כה ממושכת מנטילת התרופה ואין תאורים בספרות של הופעת AIN לאחר שנתיים מנטילת וולטרן.

11. פרופ' ויינשטיין עוד מציינת כי למעלה משנה לאחר שחרורה מהצבא, בפברואר 2019 טופלה המעוררת באנטיביוטיקה מוקסיפן במשך שבוע, וביוני 2019 טופלה בוולטרן למשך 20 יום ע"י רופא משפחה בקופת חולים. אם אכן יש בסיס לטענה ש ה AIN נגרמה מסיבה של נטילת תרופות, הרי שיותר סביר בהיבט של לוח הזמנים שטיפולים אלו בשנת 2019 הם שתורמו לכך, ובוודאי לא הטיפול שקיבלה שנתיים קודם לכן.

12. עוד מציינת פרופ' ויינשטיין, כי יש לקחת בחשבון אתיולוגיה אפשרית אחרת להתפתחות AIN והיא הזיהום בשתן עם חיידק סטרפטוקוקוס שצמח בשתי תרביות במהלך האשפוז בנובמבר 2019 אשר בגינו טופלה באנטיביוטיקה. מחוללים זיהומיים בהחלט נמצאים בין הגורמים הנפוצים להתפתחות AIN כפי שמדווח בספרות ומתבטאים בממצאי ביופסית הכליה כפי שנצפו אצל המעוררת.

13. לעניין טענת המעוררת כי שמרה בעת שהותה בכלא הצבאי תוך שהיא עם חום וכאבי גרון, ואירוע זה גרם להתפתחות אי ספיקת הכליות- פרופ' ויינשטיין מגיבה כי אינה סבירה כלל, שכן מדובר במחלה קצרת טווח שחלפה במהרה לאחר טיפול של ימים ספורים.

14. זאת ועוד, מחלת הכליות הכרונית של המעוררת נגרמה ממחלה גנטית (TSC) המאופיינת בפיברוזיס נרחב, ציסטות קטנות ונזק כרוני לרקמות הכליה. פרופ' ויינשטיין מציינת לעניין זה, כי הספרות הרפואית מבהירה שמחלה זו מתקדמת בצורה שאינה תלויה בגורמים חיצוניים.

15. פרופ' וינשטיין מתייחסת במפורש לשימוש בתרופות מסוג NSAID (וולטרן, אטופן) שניתנו למעוררת במהלך השירות ואחריו. על פי חוות דעתה, לא ניתן לקשור את הטיפול התרופתי למחלת הכליות או להחמרה במצבה.
16. אין כל ראיה רפואית התומכת בטענה כי תנאי השירות גרמו להחמרה במצבה הרפואי או תרמו למחלתה של המעוררת.
17. הספרות הרפואית תומכת בכך שAIN מופיעה לרוב בטווח זמן קצר מנטילת התרופה, בעוד שבמקרה זה של המעוררת לא נצפו סימנים קליניים או פתולוגיים לכך.
18. הביופסיה שבוצעה למעוררת אינה תואמת את המאפיינים הקליניים של AIN כגון נוכחות תסנין דלקתי או אאוזינופילים.
19. הממצאים מצביעים על נזק כרוני בלבד, שאינו קשור לשימוש בתרופות ממשפחת NSAID או אחרות.
20. פרופ' וינשטיין מצינת כי המעוררת קיבלה מינונים סבירים ובטווח בטוח לשימוש של NSAID במהלך השירות.
21. פרופ' וינשטיין מדגישה שהשפעת התרופות, אם הייתה כזו, אינה ניתנת להוכחה על סמך הממצאים הרפואיים וכי הספרות הרפואית העדכנית מצביעה על כך שמצבי AIN הנגרמת מתרופות NSAID מופיעים לרוב בגיל מבוגר יותר ובנסיבות שונות מאלו של המעוררת, ומחקרי מקרה מראים כי AIN מופיעה בטווח זמן קצר יחסית מנטילת התרופה, דבר שלא התרחש בענייננו.
22. פרופ' וינשטיין מתייחסת לחוות הדעת של ד"ר וולובסקי ודוחה את טענתו על כך שתרופות NSAID היוו גורם מרכזי בנזק לכליות זאת, בין היתר, מאחר שלא נמצאה עדות קלינית או פתולוגית התומכת בכך וכי המינונים שניתנו למעוררת היו סבירים ונמצאים בטווח הבטוח לשימוש.
23. עוד מדגישה פרופ' וינשטיין כי לא היה צורך בבדיקות דם נוספות במהלך השירות, בהתאם למצבה של המעוררת. הפרקטיקה הרפואית המקובלת אינה מחייבת מעקב בדיקות דם, וטיפול בNSAID הינו מקובל בצעירים עם כאב גרמי או חום. הטיפול שקיבלה המעוררת במהלך חודש שירותה האחרון בצבא לא דרש מעקב רפואי קפדני.
24. כמו כן, מצינת פרופ' וינשטיין כי טענתו של ד"ר וולובסקי לקיומו של AIN בעקבות שימוש בתרופות אינה מבוססת, שכן לא נצפתה נוכחות של מאפייני דלקת חריפה בבדיקות הביופסיה.
25. בנוסף, הספרות עליה הסתמך ד"ר וולובלסקי מתייחסת למצבים כלליים ואינה משקפת את המקרה הספציפי של המעוררת.
26. על פי חוות דעתה של פרופ' וינשטיין, הממצאים הפתולוגיים של המעוררת מתאימים למחלה כרונית בלבד, ולא לנזק תרופתי חריף.

27. על כן, מסקנתה של פרופ' וינשטיין כי אין קשר סיבתי בין תנאי השירות של המערערת לבין התפתחות אי ספיקת הכליות הסופנית שפיתחה כשנתיים לאחר מכן.

28. נטל ההוכחה בדבר הקשר שבין השירות לבין הפגיעה מוטל במלואו על המערערת ברמת ההוכחה הנדרשת במשפט אזרחי (רע"א 2027/94 קליג' נ' קצין תגמולים, פ"ד נ (1), ע"א 472/89 קצין תגמולים נ' רוט, פ"ד מה(5) 203 ואם מתברר בסיום הדיון כי כפות המאזניים מאוינות אזי המערערת לא עמדה בחובת ההוכחה המוטלת עליה (ע"א 192/85, קצין התגמולים נ' הכט, פ"ד מד(3), 646).

29. הנטל להוכחת הערעור מוטל כל כולו על שכמי המערערת.

30. המשיב יסתמך בערעור זה על חוות הדעת של פרופ' וינשטיין על התיק הרפואי ועל החומר הרפואי.

31. המשיב שומר לעצמו את הזכות להגיש כל חומר נוסף שיתקבל, ככל שיתקבל וכן לצרף תצהירים מטעמו.

32. המשיב שומר על זכותו לחקור את המערערת ואת המומחה מטעמה.

33. המשיב שומר על זכותו לטעון טענות נוספות, לתקן הטענות ולפרטן, לרבות טענת בחירת זכויות במל"ל והתיישנות.

אשר על כן יש לדחות את הערעור ולהטיל על המערערת הוצאות וכן שכ"ט עו"ד ומע"מ כדין.



איריס הדר אגסי מימון , עו"ד
ב"כ המשיב

תוכן עניינים

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נספח 1

חוות דעת מייעצת

עמ' 6

משרד הביטחון - אגף השקום
יחידה לתביעות תגמולים והטבות
חוות דעת רפואית באוריינטציה משפטית

פרופ' טליה וינשטיין, מומחית לנפרולוגיה ויתר לחץ דם, רשיון מס' 17912
מינבי אקדמי: פרופסור חבר קליני לרפואה פנימית, הפקולטה לרפואה ע"ש סאקלר, אוניברסיטת תל אביב

תיק מס': 713886005

הנדון: עדן יצחק ת"ז 208935874

הפגישה נערכה בנוכחות אמא של מבקשת ההכרה.

בת 26, ילידת הארץ, רווקה, סיימה תואר במשפטים.

מעברה (כפי שנמסר ע"י מבקשת ההכרה, ב-26 יולי 2023):

- היא נולדה בניתוח קיסרי עקב גודל קטן.
- לא היו אירועים מיוחדים, ללא אשפוזים או תרופות.

משפחה (כפי שנמסר ע"י מבקשת ההכרה, ב-26 יולי 2023):

- אם בת 51, בריאה.
- אב בן 54, בריא.
- אח בן 29, בריא.
- סבא מצד אמא החל טיפולי דיאליזה בגיל 52, עבר לאחר מכן השתלת کلیה.
- יש הסטוריה של מחלות ריאה במשפחה האם.

פרטי המחלה (כפי שנמסר ע"י מבקשת ההכרה, ב-26 יולי 2023):

- באוקטובר 2017 היתה 25 יום בכלא צבאי. באחד הלילות שמרה עם חום גבוה, כאבי גרון וכאבים בכל הגוף. נתנו לה אטופן ואקמול. קבלה 14 ימי גימלים.
- בערך כחודש לאחר השחרור מהכלא, חזרו כאבי הכתפיים. בביקור רופא קבלה זריקת וולטרן, שלא עזרה. היא פיתחה חום, חזרה לביקור רופא וקבלה שוב זריקת וולטרן. קבלה משככי כאבים.
- השתחררה מהצבא 3 חודשים לאחר האירוע של קבלת הזריקות.
- שנה וחצי לאחר השחרור התחילו הקאות 3-4 פעמים ביום. ביצעה בדיקות דם והודיעו לה שצריכה להגיע לחדר מיון, הגיעה למיון שיבא עם קריאטינין 9, אוראה 350. חזרו על הבדיקות כי היה נראה כטעות.
- אושפזה למשך 10 ימים, קבלה סטראואידים 60 מ"ג ליום. השתחררה, הקריאטינין לא ירד ואושפזה שוב.
- ביצעה דיאליזה למשך שנה וחצי. בפברואר 2021 עברה השתלת کلیה. הדיאליזה גרמה לפגיעה בלב, ריאות. במהלך הדיאליזה ניגשו אליה שני רופאים ואמרו לה שזריקות הוולטרן גרמו לה לכשל כליתי, ושהיא אלרגית לוולטרן.
- כעת בבקורת אחת לחודש. היא במעקב אצל רופא ריאות אחת לשנה, אקו לב פעם בשנה, MRI מוח פעם ב-3 שנים. פעם בשנה מבחן לב במאמץ.

תרופות והרגלים (כפי שנמסר ע"י מבקשת ההכרה, ב-26 יולי 2023):

סרטיקן 2 מ"ג, טאקרוסל 3.5 מ"ג 2X, מגנזיום, פרדניזון 5 מ"ג, אומפרדקס 20 מ"ג, אספירין, ויטמין D 2000 יח,

בבדיקתה (ב-26 יולי 2023):

- לחץ דם 110/65, דופק 84, סדיר.
- לב: קולות סדירים ללא אוושות או שפשוף.
- ריאות: נשימה בועית, לא חרחורים או צפצופים.
- בטן: רכה, ללא רגישות, כבד וטחול לא נמושו. צלקת ניתוחית.
- גפיים: ללא בצקת.

מסמכים רלוונטיים: תצהיר, טופס תביעה, מסמכים רפואיים שונים אשר בתיק התביעה.

שירות צבאי:

- התגייסה עם פרופיל 97 באוקטובר 2015.
- השתחררה בינואר 2018.
- באוקטובר 2017 שהתה במחבוש כ-10 ימים בכלא 4, ולאחר מכן עברה לכלא 6.

תיק רפואי:

בקורים במרפאות בצבא:

- 16.1.2018: ביקור רופא: בת 21, בריאה בדרך כלל. פנתה בשל כאב בכתף שמאל מזה כחודשיים. נבדקה על ידי אורטופד אשר התרשם מדלקת בגיד (לא הוצג מסמך רשמי). יש להפנות את החיילת לאורטופד לצורך בירור וניהול משככי כאבים. אביטרן מותר פעם ביום בלבד. ל"ד 119/80, חום 37.2.
- 31.12.2017: ביקור רופא: לדבריה סובלת מדלקות חוזרות בכתף שמאל הגיעה עם התקף של כאב. חום 36.8, ל"ד 122/82. כאבים במישוש. שוחררה עם זריקת וולטרין 75 מ"ג IM. מעקב רופא אורטופד בצבא.
- 17.12.2017: ביקור רופא: מאתמול כאב גרון. בנוסף מתארת שיעול ליחתי, ללא קוצר נשימה. נמדד בבית חום 38.2. מדדים: 37.3. לחץ דם 114/74. נינוחה, עירנית. לוע ללא אודם, שקדים מוגדלים עם תפליטים. אבחנה משוערת PHARYNGITIS. טיפול 0.5 RAFAPEN 2X 7-10 ימים.
- 13.12.2017: מחנה תל השומר, ד"ר סמירנוב: החיילת מזה חודש מתלוננת על כאבים בכתף שמאל. קבלה זריקת וולטרין עם שיפור זמני. חום 37.2. רגישות במישוש שרירים פאראוורטברלי באזור ע"ש צווארי בצד שמאל. כח גס ותחושה שמורים. להתחיל טיפול מקומי עם אסופן וולטרין. יעוץ אורטופד.
- 6.12.2017: מזה יומיים כאב גרון ונזלת, בנוסף מתארת שיעול יבש. מציינת קושי משמעותי בבליעה, בבית נמדד חום 38. בבדיקת חום 37.5. לוע: אודם, נמושו בלוטות לימפה צוואריות רגישות ומוגדלות. קולות לב סדירים, ללא אושיות, ריאות נשימה בועית ללא ממצאים דאזנתיים ממוקדים לריאות, ללא סימני גירוי מנינגיאלי. אקמיל, סינופד, רפטרצין.
- 5.12.2017: מתלוננת על כאבי גרון ונזלת ביומיים האחרונים, לא מדדה חום. במרפאה 37.1. סטרפסילס.
- 3.12.2017: ביקור רופא: מציינת לפני שבועיים כאבים בכתף שמאל, ב- INTERNAL AND EXTERNAL ROTATION כאבים, ללא הגבלה בתנועה או בעיה נוירולוגית. קבלה זריקת וולטרין 75 מ"ג IM.
- 16.11.2017: מאתמול סובלת מהקאות חוזרות. ללא עליית חום. לצי CPR נבדקה על ידי רופא, קבלה טיפול סימפטומטי. 37.1. בדיקה נוירולוגית, בדיקת לוע, ריאות, תקינים. בטן רכה, ללא גירוי ציפקי, רגישות במישוש בחלק תחתון של בטן, כבד וטחול לא נמושו. ניקוט מיתני שלילי. הומלץ על שתיה מרובה, במידה וישנה החמרה או עליית חום לשוב לבדיקה. פרמין, פפברין.
- 15.11.2017: ד"ר סמירנוב: החיילת מתלוננת על כאבי גרון וקושי בבליעה. לפני שבוע קבלה אנטיביוטיקה רוקסו לא מציינת שיפור. חום 37. שקדים מוגדלים עם אודם, ללא תפליטים, בלוטות לימפה תת ליסתיות וצוואריות לא נמושו מוגדלות. סינופד, פליקסונו.
- 8.11.2017: ביקור רופא: מזה 4 ימים כאב גרון ונזלת. בנוסף מתארר שיעול ליחתי. נמדד בבית חום 38. ללא תלונות נוספות. בבדיקת חום 36.5. ללא אודם בלוע. רושם של מחלה וירלית. במידה ויש החמרה או עליית חום מעל 38 לפנות לרופא היחידה.
- 6.11.2017: כאב גרון, נזלת שיעול ליחתי זה שבוע. חום 37.3. ליע עקד ימני מוגדל ללא תפליט. רוקסו, סולבקס, לורטידין.
- 31.10.2017: כלואה. מתלוננת מזה 5 ימים על כאבי גרון, שיעול פרודיקטיבי, נזלת, אודינופגיה אך שותה יאוכלת כרגיל. בבדיקת חובשת ללא עליית חום 37.1. נמושה בליטח לימפה מוגדלת בצוואר 0.5 ס"מ, גישה וניידת. פה ולוע ללא אדמומיות, שקדים לא מוגדלים, ללא תפליטים. בתמונה של מחולל וירלי טיפול סימפטומטי. למוסין, אקמול. קיבלה 4 ימי גימל.
- 30.10.2017: ד"ר אברבון פליקס: תלונות של צפורן חודרנית בבוהן 1 של כף רגל ימין. בבדיקה צפורן חודרנית במידה קלה בצד המדיאלי של בוהן 1 ברגל ימין, בקצה הדיסטלי ללא נפיחות או אודם. רגישות מעטה במישוש, ללא הפרשות. הוסבר לחיילת על אופציה ניתוחית או אופציה של טיפול על ידי כדוריסטית. מעוניינת בפדקוריסטית.

- 29.10.2017: מצינת שמרגישה שיש לה חום כל השבת. מעט שיעול ליחתי, נזלת מוגלתית וכאבי גרון. ללא הקאות. מצינת לפעמים סחרחורת. 36.6. למוסין, אקמול.
- 25.10.2017: החיילת הגיעה מכלא 4. מצינת שיש תור לרופאת שיניים בכלא 4, אך עברה לכאן. תראה את רופאת השיניים כאן.
- 23.10.2017: החיילת מתלוננת על תחושה של לחץ בשן בזמן אכילה מזה כשלושה ימים. מצינת שלפני שנה החלה לעשות באותה שן טיפול שורש אך לא סיימה אותו. שוללת כאבים, תופנה לרופאת השיניים.
- 18.10.2017: ד"ר חסין נינה: בריאה בדרך שלל, לא נוטלת טיפול תרופתי קבוע, לא ידוע על רגישויות, ללא בעיות רפואיות פעילות כעת. בבדיקה במצב כללי טוב. אין מניעה רפואית למעצר.

מסמכים מ"שיבא":

- 8-14.11.2019: סיכום אשפוז בפנימית א': בת 22. התקבלה בשל בחילות והקאות בשבועיים טרם קבלתה מלווים בחולשה כללית. בעיות במהלך השהות במחלקה: אי ספיקת כליות חריפה – ללא בדיקות במערכת מאז 2013. במעבדה קריאטינין 7 עם אורמיה. עברה בירור מעבדתי: פרוטאינוריה 200 מ"ג ליממה, C3 77, C4 תקין. ANA שלילי, אנטי GBM, אנטי MPO, אנטי PR3 שליליים. ANCA שלילי, וירולוגיה שלילית. US כליות הדגים כליות מוגדלות, אקוגניות, ציסטות קטנות מרובות בשתי הכליות.
- 10.11.2017: 8 גלומרולי, מתוכם 4 עם סקלרוזיס גלובלית, ו-4 תקינים. הודגם תהליך טובול-אינטרסטיציאלי עם 60% פיברוזיס ומוקדים של הסננה דלקתית - moderate. תסנין דלקתי כולל לימפוציטים, לויקוציטים ואאוזינופילים, חלק מהטובולי מראים הרחבה ציסטית. אימונופלורסנציה שלילית.
- טופלה בסולומדורל 3 ימים במינון של 250 מ"ג, ו-3 ימים בפרדניזון במינון 60 מ"ג. כמו כן נצפתה BACTERURIA: צמיחת GBS בשתי תרביות שתן. הוחל טיפול במוקסיפן במינון מותאם לתיפקוד הכליתי. כמו כן אנמיה, התקבלה עם המוגלובין 7.2 שבהמשך ירד עד 6.5, תמונה משולבת של מחסור בברזל ומחלה כרונית. טופלה בשתי מנות דם ובברזל. שוחררה עם טיפול בפרדניזון 60 מ"ג, מוקסיפן 500 מ"ג פעמיים ביום למשך 5 ימים, ארנספ, לוסק, ויטמין D. הומלץ על המשך מעקב במרפאה הנפרולוגית.
- 27.11.2019: ביקור במרפאה הנפרולוגית: ד"ר שיינברג: בבדיקות שנלקחו היום אוריה 336, קריאטינין 10.47, לויקוציטוזיס 15,000 (משני לסטראידים). רושם: מדובר באי ספיקת כליות מתקדמת ללא תגובה לטיפול בסטראידים. מופנית להמשך טיפול באשפוז. מבקש לחזור על בדיקות מעבדה. במידה ולא נראה שיפור נשקול אפשרות של renal replacement therapy.
- 27.11-1.12.2019: סיכום אשפוז בפנימית א': מוכרת למחלקתנו מאשפוז קודם עקב אי ספיקת כליות. הופנתה לאשפוז מהמרפאה הנפרולוגית. בצילום חזה תפליטים פלוירליים קטנים דו'צ' חדשים. במהלך האשפוז קבלה טיפול להיפרקלמיה (5.7), ולאור ההחמרה בתיפקוד הכליות וכן התחלה של סיבוכים כגון תפליטים פלוירליים וכן הפרעות אלקטרוליטיות הוחלט על ידי הצוות הנפרולוגי להתחיל דיאליזה באשפוז. בוצעה הכנסה של פרמקט ג'וגורלי מימין והוחל טיפול בהמודיאלזה. באשר לטיפול הסטראידלי, לאור זאת שלא הוכח שיפור תחת טיפול זה נתחיל בהורדת מינון הדרגתית. טיפולי דיאליזה ללא סיבוכים, משתחררת לביתה להמשך טיפול בדיאליזה ומעקב נפרולוגי במוסדנו.
- 23.2.2019: גירורגיה שיבא: עברה השתלת כליה.
- 11.4.2021: ד"ר שרון מיני, נפרולוגיה: ברביזה מוכונת של טריגרים למחלה אינטרסטיציאלית נמצא כי החל מ-3.12.2017 רצף פניות לשירות ביקור רופא. תחילה עקב כאב בכתף שמאל, אז טופלה בזריקת וולטרן, ימים בודדים לאחר מכן מחלת חום שיוחסה לזיהום רספירטורי ממקור עליון וטופלה אנטיביוטית (קורס קצר ב-6.12 וקורס חוזר ב-17.12). 31.12.2017 פניה חוזרת עקב כאב כתף שמאל עם הזרקה נוספת של וולטרן IM, כל זאת ללא בירור מעבדתי או הדמיתי.
- לאור סיפור של מחלת כליה משפחתית (סב מצד האם עבר השתלת כליה, סב מצד האב עבר כריתת כליה בגיל 18 מסיבה לא ידועה) נשלחה לבירור גנטי: בבדיקת clinical exome לפאנל גנים למחלות כליה נמצאה מוטציה בגן TSC1 מסוג stop codon. לסיכום: עדן אובחנה כסובלת מאי ספיקת כליות סופנית משנית למחלת Tuberous sclerosis. היא התייצגה עם ההסתמנות הכליתית הפחות שכיחה במחלה זו, קרי ציסטות מרובות קטנות עם נזק אינטרסטיציאלי. ללא אנגיוליפומות האופייניות למחלה. בהנחה שאכן תיפקוד כליתי היה שמור ב-2012, נראה כי מדובר בהתקדמות מהירה יחסית של מחלתה. יתכן שהטיפול התרופתי שקיבלה ב-12.2017 ובכללו NSAID גרם לנזק נפרוטוקסי נוסף והאיץ מהלך ההדרדרות כליתית.

דיון:

בדצמבר 2019 גב' עדן יצחק אושפזה ב"שיבא" עקב אי ספיקת כליות מתקדמת שאובחנה בבדיקות מעבדה, כאשר פיתחה תסמינים של אורמיה כשבועיים טרם אושפזה. בדיקות הדם האחרונות שנמצאו במערכת בוצעו בשנת 2012, ודווחו כתקינות. אין כל מידע על הטיפול הכליתי במהלך 7 השנים שחלפו בין שתי הבדיקות. לאור אי ספיקת הכליות הקשה היא עברה ביופסיה כלית שבוצעה באשפוז, ונמצאו שני ממצאים: א. תמונה של נפריטיס אינטרסטיציאלית; ב. פיברוזיס ניכרת של הגלומרולרי והטובולרי-אינטרסטיציאלים, בלוי ציסטות מרובות בטובלי.

מתוך מחשבה שישנו מרכיב חריף והפך למחלתה, לאור הנפריטיס האינטרסטיציאלית, היא טופלה במינון גבוה של סטרואידים, אולם לא הגיבה לטיפול זה ונזקקה לטיפול בהמודיאליזה כרונית עקב כשל כליתי. בהמשך היא אובחנה כסובלת ממחלת TSC על פי מיפוי גנטי. היא טופלה בהמודיאליזה החל מדצמבר 2019, ועברה השתלת כלית מוצלחת בפברואר 2021.

על פי התצהיר גב' יצחק טוענת לשני גורמים שהאיצו את התקדמות מחלת הכליות: ראשית, היא מציינת שסבלה ממחלת חום עם כאבי גרון בעת שהותה בכלא הצבאי באוקטובר 2017 ונאלצה לשמור במצב זה. אין זה סביר כלל שאירוע זה גרם להתפתחות אי ספיקת הכליות, מדובר במחלה קצרת-טווח שחלפה במהרה לאחר טיפול תוך ימים ספורים. כגורם עיקרי להמרת הטיפול היא מציינת כי קיבלה שתי זריקות וולטרן במהלך חודש דצמבר 2017 בשל כאבי כתפיים.

בהתייחסות לתצהיר וכן למסמכים מנפרולוגיה ב"שיבא" ארחיב על מספר נושאים שקשורים לאבחנתה של גב' עדן יצחק:

1. נפריטיס אינטרסטיציאלית חריפה (AIN – acute interstitial nephritis).
2. סוגי הפגיעה הכליתית הנובעים משימוש בתרופות non-steroidal anti-inflammatory (NSAID).
3. המעורבות הכליתית ב-TSC שגורמת להתפתחות אי ספיקת כליות.

1. **(AIN – acute interstitial nephritis):** הינה מחלה כליתית חריפה, הגורמת לעיתים קרובות להידרדרות בטיפול הכליתי. היא מאופיינת על ידי נוכחות של תסנין דלקתי בביופסיה כלית. הגורמים להתפתחותה כוללים תרופות, זיהומים ומחלות אוטואימוניות סיסטמיות (1). תרופות מהוות 70-75% מהסיבות ל-AIN. ההסתמנות הקלינית יכולה להיות א-הסמינית או עם בחילה, הקאה והרגשה כללית רעה. לעיתים קרובות קיים מופע של מחלה אלרגית: חום, פריחה, אאזינופיליה בספירת הדם ונוכחות של כדוריות דם לבנות רבות בשתן, לעיתים עם אאזינופילים (1). תמונה אלרגית זו נעדרת באופן בולט ב-AIN שנובעת מנטילת NSAID, שם התמונה האופיינית הינה פרוטאינוריה בטווח הנפרוטי, כאשר בביופסיה קיימת תמונה של minimal change disease או membranous nephropathy. התאוששות ספונטנית מתרחשת לרוב תוך שבועות או חודשים מנטילת התרופה (1). לאור העובדה שגב' יצחק קיבלה שתי זריקות וולטרן שנתיים טרם התייצגותה עם אי ספיקת הכליות, והיות והתמונה הקלינית, המעבדתית וההסטולוגית כלל לא מתאימה ל-AIN מ-NSAID (היעדר פרוטאינוריה, לויקוציטוריה וביופסיה כלית שלא תומכת באבחנה זו) – ניתן לומר שאבחנה זו אינה רלוונטית למבקשת ההכרה.

2. תרופות ממשפחת NSAID, שוולטרן נמנית עליהן, יכולות לגרום לפגיעה כליתית במספר מנגנונים ואסכם את אלה הרלוונטיים לגב' יצחק.

א. אי ספיקת כליות על רקע נפריטיס אינטרסטיציאלית חריפה (AIN-acute interstitial nephritis). כאמור לא רלוונטית למבקשת ההכרה.

ב. אי ספיקת כליות חדה על רקע המודינמי: לרוב מתגלה באופן מקרי בעת בירור של בעיה רפואית אחרת. היא מופיעה לאחר נטילה **רסנטי** של התרופה, ומתפתחת לרוב תוך 3-7 ימים מעת הנטילה (2). ההתאוששות מתרחשת לרוב תוך מספר יממות לאחר הפסקת התרופה. לנוכח העובדה שגב' יצחק קיבלה שתי זריקות וולטרן כשנתיים טרם האשפוז, הרי שמנגנון זה אינו רלוונטי.

ג. התפתחות של אי ספיקת כליות כרונית: ישנם דווחים על אסוציאציה בין **שימוש ממושך** ב-NSAID לבין התפתחות של אי ספיקת כליות כרונית, אם כי הספרות הרפואית חלוקה בנושא (3). רוב המקרים שמדווחים על קשר אפשרי מציינים שהמטופל נטל תקופה ממושכת את ה-NSAID. כך במחקר שבחן 716 מטופלים, נמצא שנטילה של לפחות 5000 כדורים היה באסוציאציה חיובית להתפתחות מחלת כליות כרונית (4). בסקירה של 583 מקרים עם אי ספיקת כליות סופנית והיסטוריה של נטילת משככי כאב שונים,

נמצא ששימוש ב-NSAID לא היה קשור כלל להתפתחות אי ספיקת הכליות הסופנית (5). מחקר שפורסם לאחרונה על 764,228 חיילים צעירים בצבא ארה"ב מצא קשר בין צריכה של מעל 7 מנות NSAID לחודש במהלך 6 חודשים לבין התפתחות אי ספיקת כליות (6). מחקר אחר בהן 1129 צרכנים של NSAID במהלך תקופה שעלתה על 48 חודשים, ונמצא שהדבר היה כרוך בהתפתחות אי ספיקת כליות עם $eGFR > 60$ מ"ל/דקה (7). אם כך, על פי הספרות המצוטטת לעיל, רק נטילה ממושכת של NSAID יכולה להוביל לפגיעה בתיפקוד הכליתי, ומבקשת ההכרה קיבלה שתי זריקות בלבד שנתיים קודם להתייצגותה.

3. **מחלת Tuberous sclerosis complex (TSC):** הינה מחלה תורשתית המערבת איברים רבים (8) ומאובחנת בוודאות בבדיקה גנטית. היא מתאפיינת בהתפתחות גידולים שפירים באיברים רבים כולל מוח, לב, כליות, עור, עיניים, ריאות וכבד. המחלה הינה בעלת שונות רבה באופן המופע שלה גם בתוך אותה משפחה. למרות שמעורבות כליתית הינה נפוצה במחלה זו, למטופלים רבים אין כלל תסמינים כליתיים. ההסתמנות הכליתית השכיחה ביותר היא נוכחות אנגייומיוליפומות, שלא היו אצל גב' עדן יצחק. ההסתמנות השנייה בשכיחותה הינה מחלה ציסטית של הכליות שמדווחת בקרב 17-45% מחולי TSC עם מעורבות כליתית. ביופסית כליה מגלה לעיתים קרובות focal segmental glomerulosclerosis, ומחלה טובולו-אינטרסטיציאלית כרונית, כנראה משנית לאובדן נפרונים (8). אצל גב' יצחק נמצאה מחלה אינטרסטיציאלית כרונית קשה עם ציסטות טובולריות רבות. וכן סקלרוזיס של מחצית מהגלמורולי. לאחרונה פורסם מאמר בעיתון נפרולוגי חשוב המתאר שתי נשים צעירות בגיל דומה לגב' עדן יצחק עם אבחנה של TSC שהתייצגו עם תמונה קלינית דומה (9). בביופסית כליה נמצאו אצל שתיהן אותם ממצאים המתוארים אצל מבקשת ההכרה. כותבי המאמר קוראים לסוג זה microcystic variant of TSC, ומציינים שיש להיות מודעים לצורה זו של המחלה שאינה נפוצה אך מובילה לאי ספיקת כליות מתקדמת ואף סופנית. במאמר עדכני אחר מצוין ש-TSC הינה מחלה נדירה, שלא תמיד מאובחנת, וכ-40% מהחולים סובלים ממחלה כליתית כרונית. הווריאנט של microcystic disease עלול לגרום להידרדרות מהירה בתיפקוד בכליתי כבר בשנות היצירה או בתחילת שנות העשרים (10).

מבקשת ההכרה פיתחה אי ספיקת כליות סופנית בדצמבר 2019. המידע היחידי על בדיקות מעבדה טרם האירוע הזה הוא שבשנת 2012 היה לה תיפקוד כליתי תקין. אין בידנו אפשרות לדעת מתי החלה ההידרדרות בתיפקוד הכליתי שהובילה, למרבה הצער, לצורך בטיפול דיאליזה ולאחר מכן להשתלת כליה. אולם על פי המהלך הקליני, ממצאי ביופסית הכליה, והספרות הרפואית המצוטטת לעיל, מחלת הכליות הכרונית של גב' עדן יצחק נובעת ממחלת ה-TSC ולא מגורם אחר.

סיכום:

לאור האמור לעיל, נראה שאין קשר סיבתי בין תנאי השירות של גב' עדן יצחק לבין התפתחות אי ספיקת הכליות הסופנית שפיתחה כשנתיים לאחר שחרורה.

הריני מצהירה בזאת, כי ידוע לי היטב שלעניין הוראת החוק הפלילי בדבר עדות שקר בשבועה בבית משפט, דין תעודה זאת כשהיא חתומה על ידי, כדין עדות בשבועה שנתתי בבית המשפט.

תאריך: 14 אוקטובר 2023

חתימה: פרופ' טליה וינשטיין



פרופסור טליה וינשטיין
מומחית לנפרולוגיה
וינשטיין-לוקר
מ.ר. 17912
10665

במלץ לקבל מסקנות חנוכה

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2. UpToDate: NSAIDs: Acute kidney injury. Literature review current through: Oct 2023
3. UpToDate: Epidemiology and pathogenesis of analgesic-related chronic kidney disease. Literature review current through: Oct 2023
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נספח 2

החלטת קצין תגמולים

עמ' 13



היחידה לתביעות וקביעת זכאות
בכל בירור/פניה נא לציין מספר תיק



מדינת ישראל
משרד הביטחון



משרד החינוך

ב' אדר א' תשפ"ד
11 פברואר 2024

מספר תיק: 713886005
מספר זהות: 208935874

לכבוד
עדן יצחק
שואל המלך 3
קרית אונו 5565403

שלום רב,

הנדון: בקשתך להכרת זכות נכה מתאריך 22/07/2021 - החלטה

הנני להודיעך כי בקשתך נדחתה, לאחר שהגעת למסקנה, על בסיס החומר העובדתי והרפואי שעמד בפני ולרבות חוות הדעת מתאריך 14/10/2023 של פרופ' טליה וינשטיין, כי לא הוכח קשר סיבתי בין תנאי שירותך הצבאי, לרבות השהייה בכלא, לבין מחלת הכליות הכרונית בה לקית, כשנתיים לאחר שחרורך הצבאי, שהינה על רקע מחלת TSC בה לקית.

הנך רשאית לערער על ההחלטה האמורה בפני ועדת הערעורים תוך 60 יום מיום קבלתה.

את הערעור יש להגיש ב- 4 עותקים למזכירות ועדת הערעורים, לפי הכתובת: יו"ר ועדת הערעורים לפי חוק הנכים, בית משפט השלום תל אביב, רח' ויצמן 1. אם הנך זקוקה להארכת מועד להגשת ערעור עליך לפנות ליו"ר ועדת הערעורים שלו הסמכות להחליט על כך על פי חוק.

לאור האמור לעיל, זכאותך לטיפול רפואי בגין פגימה זו מסתיימת בסוף החודש העוקב לחודש זה.

מצ"ב חוות דעת רפואית כולל העתק לעו"ד מייצג.

בכבודך,

גלית טאוב
קצינת תגמולים

העתקים:

מחוז שיקום דן נכים

עו"ד אריאל פרייברג אבא הלל 7 רמת גן 5252204

בית גנזים- תיק רפואי סרוק

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נספח 3

חוות דעת מגיבה

עמ' 15

משרד הביטחון - אגף השקום
חידה לתביעות תגמולים והטבות
חוות דעת רפואית באוריינטציה משפטית

פרופ' טליה וינשטיין, מומחית לנפרולוגיה ויתר לחץ דם, רשיון מס' 17912
מינני אקדמי: פרופסור חבר קליני לרפואה פנימית, הפקולטה לרפואה ע"ש סאקלר, אוניברסיטת תל אביב

תיק מס': 713886005

הנדון: עדן יצחק ת"ז 208935874

חוות דעת זו הינה במענה לחוות הדעת של ד"ר וולבלסקי מתאריך 26 באוגוסט 2024.

ראשית, אסקור בקצרה את הפרטים הרלוונטיים הקשורים למחלתה של גב' עדן יצחק כפי שמתועד בתיק הרפואי. בנוסף, מצרפת תיעוד של ביקורים במרפאת קופת חולים לאחר שחרורה בינואר 2018 ועד לאשפוזו בנובמבר 2019. פרטים אלה לא היו ידועים לי בעת כתיבת חוות דעתי הראשונה. המידע העולה מביקורים אלה הינו משמעותי ביותר בקביעת סיבות אפשריות להתפתחות אי ספיקת הכליות של גב' יצחק.

ביקורים במרפאת בעת השירות הצבאי:

- 16.1.2018: ביקור רופא: בת 21, בריאה בדרך כלל. פנתה בשל כאב בכתף שמאל מזה כחודשיים. נבדקה על ידי אורטופד אשר התרשם מדלקת בגיד (לא הוצג מסמך רשמי)... אביטרן כדור אחד בלבד. ל"ד 119/80, חום 37.2.
- 31.12.2017: ביקור רופא: לדבריה סובלת מדלקת חוזרות בכתף שמאל. הגיעה עם התקף של כאב. חום 36.8, ל"ד 122/82. כאבים במישוש. שוחררה עם זריקת וולטרן 75 מ"ג IM. מעקב רופא אורטופד בצבא.
- 17.12.2017: ביקור רופא: מאתמול כאב גרון. בנוסף מתארת שיעול ליחתי, ללא קוצר נשימה. נמדד בבית חום 38.2. מדדים: 37.3. לחץ דם 114/74. שקדים מוגדלים עם תפליטים. אבחנה משוערת Pharyngitis. טיפול Rafapen 500 מ"ג פעמיים ביום ל-10 ימים.
- 13.12.2017: מחנה תל השומר, ד"ר סמירנוב: החיילת מזה חודש מתלוננת על כאבים בכתף שמאל. קבלה זריקת וולטרן עם שיפור זמני. חום 37.2. רגישות במישוש שרירים פאראוורטברלי באזור ע"ש צווארי בצד שמאל. כח גס ותחושה שמורים. להתחיל טיפול מקומי עם וולטרן. יעוץ אורטופד. אטופן 600 מ"ג פעם ביום ל-10 ימים.
- 3.12.2017: ביקור רופא: מצינת לפני שבועיים כאבים בכתף שמאל, ב- Internal and External rotation כאבים, ללא הגבלה בתנועה או בעיה נוירולוגית. קבלה זריקת וולטרן 75 מ"ג IM.
- 6.11.2017: כאב גרון, נזלת שיעול ליחתי זה שבוע. חום 37.3. לוע שקד ימני מוגדל ללא תפליט. רוקטו 150 מ"ג פעמיים ביום ל-5 ימים, סולבס, לורטדין.

מסמכים מ"שיבא":

- **8-14.11.2019:** אשפוז בפנימית א': בת 22. התקבלה בשל בחילות והקאות בשבועיים טרם קבלתה מלווים בחולשה כללית. בעיות במהלך השהות במחלקה: אי ספיקת כליות ודריפה – ללא בדיקות במערכת מאז 2013. במעבדה קריאטינין 7 עם אורמיה. עברה בירור מעבדתי: פרוטאינוריה 200 מ"ג ליממה, C3 77, C4 תקין. ANA שלילי, אנטי GBM, אנטי MPO, אנטי PR3 שליליים. ANCA שלילי, וירולוגיה שלילית. US כליות הדגים כליות מוגדלות, אקוגניות, ציסטות קטנות מרובות בשתי הכליות.
- ביופסית כליה ב-10.11.2017: 8 גלומרולי, מתוכם 4 עם סקלרוזיס גלובלית, ו-4 תקינים. הודגם תהליך טובול-אינטרסטיציאלי עם 60% פיברוזיס ומוקדים של הסנגה דלקתית - moderate. תסנין דלקתי כולל לימפוציטים, לויקוציטים ואאחינופילים רבים, חלק מהטובולי מראים הרחבה ציסטית. יש אטרופיה טובולרית ומוקדים רבים של אטרופיה טובולרית וטובוליטי mild to moderate. כלי דם עם הרחבה של האינטרמיה. אימונופלורסנציה שלילית.
- כמו כן נצפתה Bacteruria: צמיחת Group B Streptococcus בשתי תרביות שתן. הוחל טיפול במקסיפן במינון מותאם לתיפקוד הכליתי.
- **11.4.2021:** ד"ר שרון מיני, נפרולוגיה: ברביחיה מוכוונת של טריגרים למחלה אינטרסטיציאלית נמצא כי החל מ-3.12.2017 רצף פניות לשירות ביקור רופא. תחילה עקב כאב בכתף שמאל, אז טופלה בזריקת וולטרן, ימים בודדים לאחר מכן מחלת חום וטופלה אנטיביוטית (קורס קצר ב-6.12 וקורס חוזר ב-17.12).
- 31.12.2017 פניה חוזרת עקב כאב כתף שמאל עם הזרקה נוספת של וולטרן IM. עדן אובחנה כסובלת מאי ספיקת כליות סופנית משנית למחלת Tuberous sclerosis. היא התייצגה עם ההסתמנות הכליתית הפחות שכיחה במחלה זו, קרי ציסטות מרובות קטנות עם נוק אינטרסטיציאלי. בהנחה שאכן תיפקוד כליתי היה שמור ב-2012, נראה כי מדובר בהתקדמות מהירה יחסית של מחלתה. יתכן שהטיפול התרופתי שקיבלה ב-12.2017 ובכללו NSAID גרם לנזק נפרוטוקסי נוסף והאיץ מהלך הדרדרות כליתית.

להלן מידע שלא היה בידי בעת כתיבת דו"ח הדעת הראשונה:

ביקורים במרפאת "מכבי":

- **25.2.2019:** ד"ר לובוצקי: זיהום בדרכי הנשימה העליונות. מתן מוקסיפן (Amoxicillin) 500 מ"ג 3X ליום במשך שבוע.
- **1.7.2019:** ד"ר לובוצקי: אתמול נפלה מקורקינט ונחבלה בחלקי גוף שונים, מכות יבשות וכוואבות. אין עדות לפגיעה גרמית, פצעי שפשוף חבושים. מתן Etodolac (Etodolac) 500 מ"ג פעם ביום למשך 20 ימים.

דיון:

בנובמבר 2019 גב' עדן יצחק אושפזה ב"שיבא" עם אי ספיקת כליות מתקדמת שאובחנה בבדיקות מעבדה, לאחר שפיתחה תסמינים של אורמיה כשבועיים טרם אשפזה. בדיקות הדם האחרונות שנמצאו במערכת בוצעו בשנת 2012, ודווחו כתקינות. אין כל מידע על התיפקוד הכליתי במהלך 7 השנים שחלפו בין 2012-2019.

לאור אי ספיקת הכליות הקשה היא עברה בירור יסודי שכלל בדיקות דם ושתן, אולטרה-סאונד כליות וביופסית כליה. בביופסיה נמצאו שני ממצאים עיקריים:

א. תמונה של נפריטיס אינטרסטיציאלית;

ב. פיברוזיס ניכרת של הגלומרולרי (50%) והטובולו-אינטרסטיציום (60%), ונוכחות של ציסטות מרובות בטובולו-אינטרסטיציום.

אבחנת העבודה של המחלקה היתה שקיים מרכיב חריף והפך, לפחות חלקית, למחלתה, לאור נוכחות של גפריטיס אינטרסטיציאלית, היא טופלה במינון גבוה של סטרואידים, אולם לא הגיבה לטיפול זה ולכן נזקקה לטיפול בהמודיאליזה החל מדצמבר 2019, ובפברואר 2021 עברה השתלת כליה מוצלחת. לנוכח הממצאים הציטיים הרבים בכליה בביופסיה ובהדמית אולטרה-סאונד בוצע בירור גנטי והיא אובחנה כסובלת ממחלת tuberous sclerosis complex (TSC).

גב' יצחק טוענת שהגורם העיקרי להתפתחות אי ספיקת הכליות הינה טיפול ב- non-steroidal anti-inflammatory drugs (NSAID) במהלך חודש דצמבר 2017. בחוות דעתו ד"ר וולבלסקי תומך בטענה זו.

בהתייחסות למהלך הקליני וממצאי הביופסיה ארזיב על הסיבות האפשריות לכשל הכליתי אצל גב' עדן יצחק:

1. גפריטיס אינטרסטיציאלית חריפה (acute interstitial nephritis – AIN).

2. מעורבות כליתית ב-TSC שגורמת למק רקמתי והתפתחות אי ספיקת כליות.

פרוט:

1. AIN הינה מחלה חריפה, הגורמת לעיתים קרובות להידרדרות בתיפקוד הכליתי. היא מאופיינת על ידי נוכחות של תסנין דלקתי ואאוזינופילים בביופסיה כלית (1). מתוך שלל הסיבות המובילות ל-AIN ישנן שתיים שיכלו לגרום לכך אצל גב' יצחק: תרופות וזיהומים (1,2). בספרות הרפואית מקובל שתופות מהוות 70-75% מהסיבות ל-AIN (1,2). ההסתמנות הקלינית יכולה להיות א-תסמינית או להופיע עם בחילה, הקאה והרגשה כללית רעה. לעיתים קרובות קיים מופע של מחלה אלרגית: חום, פריחה, אאוזינופיליה בספירת הדם ונוכחות של כדוריות דם לבנות רבות בשתן, לעיתים עם אאוזינופילים (2). תמונה אלרגית זו נעדרת באופן בולט ב-AIN שנובעת מנטילת NSAID, שם התמונה האופיינית הינה פרוטאינוריה משמעותית, כאשר בביופסיה קיימת לעיתים קרובות תמונה של minimal change disease או membranous nephropathy (1). בסקירות עדכניות על AIN בעקבות נטילת NSAID הגרמת לאי ספיקה כליתית חריפה מציינת שהיא מופיעה לרוב בגיל מבוגר יותר, נעדרת התמונה הקלאסית של נוכחות אאוזינופילים בביופסיה כלית, וזמן החציון מנטילת התרופה עד להופעת AIN הוא 3 חודשים (3,4).

ההתאוששות הינה ספונטנית ומתרחשת לרוב תוך שבועות או חודשים לאחר נטילת התרופה (1):

"Renal pathology usually shows cytotoxic T-cell with a paucity of eosinophils, which is notably different from classic AIN from other medications. The median age of patients with NSAIDs induced AIN is around 50 years. Patients with NSAIDs induced AIN may concomitantly develop nephrotic syndrome but frequently have sub nephrotic range proteinuria with median urine protein of 1.1 g/d. The median time of exposure is 3 months before the diagnosis.(3)"

גב' יצחק טופלה בשתי זריקות וולטרן במהלך השירות הצבאי כשנתיים טרם התייצגותה עם אי ספיקת הכליות, כך שאין זה סביר כלל ש-AIN הופיעה לאחר תקופה כה ממושכת מנטילת התרופה. אין תיאורים בספרות של הופעת AIN לאחר שנתיים מנטילת וולטרן.

אולם חשוב מכך: למעלה משנה לאחר שחרורה מהצבא, בפברואר 2019 היא טופלה באנטיביוטיקה מוקסיפן (Amoxicillin) במשך שבוע, וביוני 2019 טופלה בחולטרן (Diclofenac) למשך 20 יום על ידי רופא המשפחה בקופת החולים. במידה ואכן ה-AIN נגרמה מסיבה תרופתית, הרי שיותר סביר בהיבט של לוח הזמנים שטיפולים אלה בשנת 2019 תרמו לכך, ובודאי לא הטיפול שקבלה שנתיים קודם לכן.

אך חשוב לקחת בחשבון שקיימת גם אתילולוגיה אפשרית אודות להתפתחות AIN והיא הזיהום בשתן עם החידק group B streptococcus שצמח בשתי תרביית בעת האשפוז בנובמבר 2019, ובגיון טופלה באנטיביוטיקה. מחוללים זיהומיים בהחלט נמצאים בין הגורמים הנפוצים להתפתחות AIN כפי שמדווח בסקירות שונות ומתבטאים בממצאים דומים בביופסיה הכליה כפי שנצפה אצל גב' יצחק (1-4).

2. מחלת Tuberous sclerosis complex: הינה מחלה תורשתית המערכת איברים רבים (5) ומאובחנת

בוודאות בבדיקה גנטית. היא מתאפיינת בהתפתחות גידולים שפירים באיברים רבים כולל מוח, לב, כליות. למרות שמעורבות כליתית הינה נפוצה במחלה זו, למטופלים רבים אין כלל תסמינים כליתיים. ההסתמנות הכליתית השכיחה ביותר היא נוכחות אנגייומיוליפומות, שלא בצפו אצל גב' עדן יצחק. ההסתמנות השנייה בשכיחותה הינה מחלה ציסטית של הכליות שמדווחת בקרב 17-45% מחולי TSC עם מעורבות כליתית. ביופסיה כליתית מגלה focal segmental glomerulosclerosis, ומחלה טובול-אינטרסטיציאלית כרונית, כנראה משנית לאובדן נפרונים (5). אצל גב' יצחק נמצאה מחלה טובול-אינטרסטיציאלית כרונית קשה עם ציסטות טובולריות רבות, וכן סקלרוזיס של מחצית מהגלמולולי. לאחרונה פורסם מאמר בעיתון נפרולוגי חשוב המתאר שתי נשים צעירות בגיל דומה לגב' עדן יצחק עם אבחנה של TSC שהתייצגו עם תמונה קלינית דומה (6). בביופסיה כליתית נמצאו אצל שתיהן אותם ממצאים המתוארים אצל גב' יצחק, וכותבי המאמר נוקבים בשם microcystic variant of TSC ומציינים שיש להיות מודעים לצורה זו של המחלה שאינה נפוצה אך מובילה לאי ספיקת כליות מתקדמת ואף סופנית. במאמר עדכני אחר מצוין ש-TSC הינה מחלה נדירה, שלא תמיד מאובחנת, וכ-40% מהחולים סובלים ממחלה כליתית כרונית. הווריאנט של microcystic disease עלול לגרום להידרדרות מהירה בתיפקוד הכליתי כבר בשנות העשרה או בתחילת שנות העשרים (6).

גב' יצחק פיתחה אי ספיקת כליות סופנית בדצמבר 2019. המידע היחיד על בדיקות מעבדה טרם האירוע הזה הוא שבשנת 2012 היה לה תיפקוד כליתי תקין. אין בידנו אפשרות לדעת מתי החלה ההידרדרות בתיפקוד הכליתי שהובילה, למרבה הצער, לצורך בטיפול דיאליזה ולאחר מכן להשתלת כלית. אולם על פי המהלך הקליני, ממצאי ביופסיה הכלית, והספרות הרפואית המצוטטת לעיל, מחלת הכליות הכרונית של גב' עדן יצחק נובעת בבסיסה ממחלת ה-TSC והמחלה החריפה של נפריטיס אינטרסטיציאלית יכולה היתה לנבוע מהטיפול במוקסיפן (Amoxicillin), וחולטרן (Diclofenac) או זהו חידקי בשתן עם Streptococcus שנתגלה בעת אשפחה.

בהתייחסות ספציפית לחוות דעתי של ד"ר וולבלסקי:

- ראשית, אני מבקשת לחדד שוב את אשר כתבתי בחוות דעתי הראשונה. לא כתבתי ש"התמונה הקלינית, המעבדתית וההסטולוגית אינה מתאימה ל-AIN". נהפוך הוא, ציינתי שהיו שני מרכיבים בביופסיה:

מחלה חריפה של נפריטיס אינטרסטיציאלית ומחלה כרונית. ציטטתי את כל הממצאים כולל ביופסית הכליה, וכן את הטיפול בסטרואידים שהוענק לגב' יצחק בבסיון להתגבר על המרכיב החריף של מחלתה. מסקנתי היתה שאי ספיקת הכליות הסופנית לא נגרמה בסופו של דבר כתוצאה מהטיפול ב-NSAID כשנתיים קודם לאשפוז, אלא מהמחלה הבסיסית הכרונית שנובעת מ-TSC כפי שבאה לידי ביטוי בתמונה ההסטולוגית הקשה של פיברוזיס כליתית.

- בסעיף נוסף ד"ר וולובלסקי כותב כי קבעתי ש"לא היתה דלקת חריפה באירוע הנדון". כלל לא כתבתי דברים אלה בחוות הדעת. כן כתבתי מענה לסוגיה נוספת שהעלתה גב' יצחק בתצהיר: "מציינת שסבלה ממחלת חום עם כאבי גרון בעת שהותה בכלא הצבאי באוקטובר 2017 ונאלצה לשמור במצב זה. אין זה סביר כלל שאירוע זה גרם להתפתחות אי ספיקת הכליות, מדובר במחלה קצרת-טווח שחלפה במהרה לאחר טיפול תוך ימים ספורים."

- ד"ר וולובלסקי כותב שגב' יצחק קיבלה טיפול ב-NSAID בתדירות גבוהה, דבר שאינו מדויק. היא כן קבלה תרופות אלה במהלך חודש דצמבר 2017, אולם מאז ועד שחרורה לא קבלה אותן פעם נוספת. הוא מציין שנטלה 30 כדורים של NSAID אולם בתיקה הרפואי קיים תיעוד שונה: פעמיים קבלה כדור בודד של Abitren, ופעם אחת 10 כדורים של Etopan.

- בניגוד למה שכתב ד"ר וולובלסקי אין קיום מנחים הממליצים על הצורך בבדיקות דם לאחר מתן NSAID במטופלים בגילה של גב' עדן יצחק, אלא רק באנשים מבוגרים הרבה יותר הסובלים ממחלות כרוניות דוגמת סוכרת, אי ספיקת לב וכ"ו. משפחת תרופות זו הינה הנפוצה ביותר בטיפול בכאב ולהורדת חום באוכלוסיה הכללית וכן בצבא. בטוחני שד"ר וולובלסקי בעצמו, כרופא ילדים, אינו בודק תפקודי כליה או שולח לאולטרה-סאונד כל ילד או מתבגר שהוא רושם לו Nurofen, ממשפחת NSAID שהינו הטיפול הנפוץ ביותר להורדת חום בגילאים אלה. יתרה מזאת, זוהי התרופה המומלצת כקו ראשון להורדת חום כפי שפורסם בקווים המנחים העדכניים ב-UptoDate:

For children ≥ 6 months of age in whom antipyretic and anti-inflammatory activity are desired we suggest oral ibuprofen as the initial antipyretic agent (7).

- ולראיה, רופא המשפחה לא מצא לנכון לבצע בדיקות אלה בחודש יולי 2019 לאחר רישום Etopan למשך 20 יום.

- ד"ר וולובלסקי מצטט לכאורה את ד"ר מיני הנפרולוגית ב"שיבא": ככל הנראה, התרופות מסוג NSAID (וולטרן) הביאו לפגיעה מלייתית ואילי האיצו הזדדרדות כליתית". אולם למעשה הנוסח המדויק של ד"ר מיני הוא אחר לחלוטין (עורך הדין של גב' יצחק מצטט במדויק): "יתכן שהטיפול התרופתי שקבלה בדצמבר 2017 ובכלל NSAID גרם לבזק נפרוטוקסי נוסף והאיץ מהלך הזדדרדות כליתית". יש לשער שד"ר מיני כתבה זאת משום שגב' יצחק נחשפה למספר תרופות כולל שני סוגי אנטיביוטיקה - מוקסיפן ורוקסו - ובנוסף גם ל-NSAID. חשוב לציין שד"ר מיני ויתר הצוות לא היו מודעים לעובדה שגב' יצחק טופלה בתרופות אלה כארבעה חודשים טרם אשפוז.

- ד"ר וולובלסקי מציין שבעת האשפוז בנובמבר 2019 לא היה גורם זיהומי משמעותי שתורם למחלה, אך בסכום מהאשפוז כתוב בבירור שהיו שתי תרבויות שתן חיוביות ל-Group B Streptococcus, שאף טופלו באנטיביוטיקה, ומכאן שהן היו בעלות משמעות קלינית. לציין שנוכחות גלילי כדוריות דם לבנות בשתן אופיינית לזיהום בדרכי השתן מסוג זה ולא רק לנפריטיס אינטרסטיציאלית.

- באבחנה מבודלת של נפריטיס אינטרסטיציאלית ידוע שזיהום חיידקי יכול לגרום למחלה כפי שכתוב בגרסה העדכנית של UptoDate (1), וכן בסקירות עדכניות על הנושא (2,3):
- Acute interstitial nephritis is a kidney lesion that typically causes a decline in kidney function and is characterized by an inflammatory infiltrate in the kidney interstitium. It is most often induced by drug therapy. AIN is also caused by...a variety of infections remote to the kidney (eg, *Legionella*, leptospirosis, and streptococcal organisms).
המנגנון המשוער להתפתחות נפריטיס אינטרסטיציאלית בעקבות זיהום ב-Streptococcus הינו hypersensitivity reaction (8).
- בסכום ד"ר וולבלסקי מתייחס למספר נקודות שלהבנתו תומכות ב-NSAID כגורם לכשל הכליתי:
 - ממצא של כליות גדולות בהדמיית אולטרה-סאונד היכול לנבוע מתהליך חריף שמתרחש בהן, אולם זוהי רק אחת מהסיבות לכליות גדולות. ישנם מספר מצבים ידועים בהם הכליות סובלות מכשל סופני והן בכל זאת בגודל תקין, דוגמת מחלת הסוכרת, ומחלה ציסטית – כפי שיש לגב' יצחק. גודל הכליות אינו מהווה כלל אמצעי להעמדת אבחנה.
 - תלונה של השתנה תכופה מאפיינת כל מטופל עם אי ספיקת כליות מתקדמת הנובעת ממחלה אינטרסטיציאלית (חריפה וכרונית מסיבה כלשהי) לאור ירידה ניכרת ביכולת ריכוז השתן בשלב זה. תסמין זה אינו מהווה הסבר לקיום אבחנה ספציפית כלשהי.
 - נוכחות של אאוזינופילים בביופסית כליה בהחלט תומכת באבחנה של נפריטיס אינטרסטיציאלית, אך הדבר אינו תומך דווקא בסיבה תרופתית כפי שציינתי. למעשה נוכחות אאוזינופילים אינה שכיחה בנפריטיס כתוצאה מנטילת NSAID אלא דווקא יותר מאנטיביוטיקה (2).
 - ד"ר וולבלסקי כותב שקבלת וולטרן בדצמבר 2017 היה הגורם לכשל הכליתי לדעתם של הנפרולוגים ב"שיבא" לאורך כל המהלך הרפואי. אולם הדבר אינו מהווה הוכחה שאכן זו הסיבה לכשל הכליתי. בבואנו להתייחס למידע חדש שנתברר לאחר כתיבת חוות הדעת הראשונה, הרי שבסקירת ביקוריה במרפאה כשנה לאחר שחרורה מהצבא נמצא שטופלה 10 חודשים טרם לאשפוז במקסיפן במשך 5 ימים, וארבעה חודשים קודם לאשפוז באטופן במשך 20 יום.
- ד"ר וולבלסקי מדגיש "נקודה קריטית" בנוגע לטיפול שקיבלה גב' יצחק, והיא אי ביצוע בדיקות דם לאחר קבלת וולטרן, והוא מציין ש"זוהי סטיה מהסטנדרט הרפואי המקובל". אני חולקת על הצהרה זו. כפי שכתבתי, טיפול ב-NSAID הינו מקובל ביותר בצעירים עם כאב גרמי או חום. הטיפול שקיבלה במהלך חודש שירותה אחרון בצבא לא דרש מעקב רפואי קפדני.
- ד"ר וולבלסקי כותב שהמופיע של TSC אצל גב' יצחק אינו שכיח, ונכון הדבר. אך בספרות על TSC מתוארות תסמונות נפוצות פחות מהגידולים השפירים הרבים שנמצאים בצורה הקלאסית, ובהן מתוארת מחלה עם נוכחות של ציסטות טובולריות רבות המופיעות יחד עם פיברוזיס אינטרסטיציאלית משמעותית. הסתמנות זו הינה אופיינית לוריאנט CYSTIC DISEASE של TSC (5,6). לעיתים מתואר FSGS משני שלא נמצא אצל גב' יצחק, אולם כן נמצא אצל global sclerosis של 50% מן הגלומרולי, שמהווה למעשה התקדמות טבעית של FSGS משני. אחד מהמובילים העולמיים בתחום זה, Bissler, כותב במאמר עדכני כי עוצמת המחלה הציסטית אינה מוערכת דיה וכי בצורה המקרוציסטית (כמו של גב' יצחק) צעירים בשנות העשרה ושנות העשרים המוקדמות מפתחים אי ספיקת כליות משמעותית (9). ההסטולוגיה

בביופסית הכליה של גב' יצחק מדגימה באופן ברור כי קיימת מחלה כליתית כרונית משמעותית עם פיברוזיס נרחב של המשתית ושל הגלומרולי, וזאת בתוספת למרכיב של מחלה חריפה כפי שתואר. הבדיקה הגנטית העמידה אבחנה חד משמעית.

אני חולקת על הסיכום של ד"ר ורלובלסקי: "הפגיעה הכליתית של עדן נגרמה בסבירות גבוהה כתוצאה מחשיפה לתרופות NSAID במהלך שירותה הצבאי, ולא באופן בלעדי ממחלת ה-TSC".
ראשית, היא טופלה באנטיביוטיקה מסוג מוקסיפן בחודש פברואר 2019, וכן טופלה בוולטרן בחודש יולי 2019. בנוסף, בעת האשפוז בנובמבר 2019 סבלה מזיהום בדרכי השתן עם חיידק Group B Streptococcus. שלושת הגורמים הללו הם מחוללים שיכלו לגרום לתמונה של נפריטיס אינטרסטיציאלית חריפה.
באם נסיף לכך את העובדה שטופלה ב-NSAID בחודש דצמבר 2017, כשנתיים טרם אשפוזו עם כשל כליתי, ובנוסף אובחנה עם מחלה תורשתית שגורמת לאי ספיקת כליות – הרי שאין בסיס רפואי לטענה שהטיפול ב-NSAID בעת השירות הצבאי גרם להתפתחות אי ספיקת כליות סופנית.

סיכום:

לאור האמור לעיל, אין קשר סיבתי בין תנאי השירות של גב' עדן יצחק לבין התפתחות אי ספיקת הכליות הסופנית שפיתחה כשנתיים לאחר מכן.

הריני מצהירה בזאת, כי ידוע לי היטב שלעצמין הוראת החדק הפלילי בדבר עדות שקר בשבועה בבית משפט, דין תעודה זאת כשהיא חתומה על ידי, כדין עדות בשבועה שנתיי בבית המשפט.



חתימה: פרופ' תליה וינשטיין

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Clinical manifestations and diagnosis of acute interstitial nephritis

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All topics are updated as new evidence becomes available and our [peer review process](#) is complete.

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INTRODUCTION

Acute interstitial nephritis (AIN) is a kidney lesion that typically causes a decline in kidney function and is characterized by an inflammatory infiltrate in the kidney interstitium [1]. It is most often induced by drug therapy. AIN is also caused by autoimmune disorders or other systemic disease (eg, systemic lupus erythematosus [SLE], Sjögren's disease, sarcoidosis), a variety of infections remote to the kidney (eg, *Legionella*, leptospirosis, and streptococcal organisms), immunoglobulin G4 (IgG4) disease, and tubulointerstitial nephritis with uveitis (TINU) syndrome [2-10]. An overview of the clinical manifestations and diagnosis of AIN is presented in this topic review. The treatment of AIN is discussed separately. (See "Treatment of acute interstitial nephritis".)

Interstitial nephritis associated with SLE, sarcoidosis, the TINU syndrome, and Sjögren's disease is also discussed elsewhere.

- (See "Lupus nephritis: Diagnosis and classification", section on 'Tubulointerstitial lesions'.)
- (See "Tubulointerstitial nephritis and uveitis (TINU syndrome)".)
- (See "Kidney disease in primary Sjögren's disease".)
- (See "Kidney disease in sarcoidosis".)

ETIOLOGY

In initial reports, the vast majority of cases of AIN resulted from exposure to beta-lactam antibiotics, particularly methicillin. However, drugs other than antibiotics, as well as infections and other underlying conditions, are also recognized as clinically significant causes.

The distribution of causes of AIN has been reported as follows [6,9,11-13]:

- Drugs – 70 to 75 percent (with antibiotics responsible for approximately 30 to 50 percent of these cases)
- Systemic disease including sarcoidosis, Sjögren's disease, systemic lupus erythematosus (SLE), and others – 10 to 20 percent
- Infections – 4 to 10 percent
- Tubulointerstitial nephritis and uveitis (TINU) syndrome – less than 5 percent

Drugs — Virtually any drug can cause AIN, although only a few have been reported with any frequency. While there are single case reports of many drugs associated with AIN, we attribute cause to a previously unreported drug only when the study reports that AIN was confirmed by kidney biopsy and the patient was not concomitantly taking other drugs that can cause AIN. In many cases, a causal link with the drug is established by observing the onset of kidney function impairment after initiating the drug and its resolution after discontinuing the drug.

On the other hand, it may be difficult to identify the culprit drug in some patients with biopsy-proven AIN who are taking multiple medications.

AIN was particularly common with methicillin, occurring in up to 17 percent of patients who had been treated for more than 10 days [5,14,15]. Methicillin is no longer manufactured.

Other common drugs that cause AIN include [2-4,13,15-29]:

- Nonsteroidal antiinflammatory agents (NSAIDs), including selective cyclooxygenase (COX)-2 inhibitors
- Penicillins and cephalosporins
- Rifampin
- Antimicrobial sulfonamides, including trimethoprim-sulfamethoxazole
- Ciprofloxacin and, perhaps to a lesser degree, other quinolones
- Diuretics, including loop diuretics such as furosemide and bumetanide, and thiazide-type diuretics
- Cimetidine (only rare cases have been described with other H-2 blockers such as ranitidine)
- Allopurinol
- Proton pump inhibitors (PPIs) such as omeprazole and lansoprazole
- 5-aminosalicylates (eg, mesalamine)
- Anticancer drugs, such as immune checkpoint inhibitors (ICPi; such as ipilimumab and nivolumab)

The development of drug-induced AIN is not dose-dependent, and a recurrence or exacerbation of AIN can occur with a second exposure to the same or a related drug [30].

Several studies have shown an association between PPIs and AIN [26-29].

(See "Proton pump inhibitors: Overview of use and adverse effects in the treatment of acid related disorders", section on 'Kidney disease'.)

AIN can be a common complication among patients with inflammatory bowel diseases (IBD). In most patients with IBD, AIN has been attributed to treatment with 5-aminosalicylates [31,32], although AIN has also been described in treatment-naïve patients [33].

Different types of anticancer drugs can cause AIN [34]. AKI has been reported in approximately 1 to 5 percent of patients receiving an ICPI (ie, ipilimumab, nivolumab, pembrolizumab, atezolizumab); AIN is the most common type of kidney pathology in such patients [35-40]. In the largest observational study of ICPI-associated AKI, 93 percent of the patients biopsied had AIN [39]. Median time of onset of AKI was 14 weeks (interquartile range 6 to 37 weeks). A lower baseline estimated glomerular filtration rate, concomitant use of PPIs, and combination therapy with different ICPIs were independently associated with an increased risk of developing AKI. The vast majority of patients stopped the ICPI (97 percent) and were treated with glucocorticoids (86 percent). Complete or partial recovery was observed in 85 percent of patients. Re-introduction of the ICPI led to a recurrence of AKI in only 23 percent of patients. Additional details of kidney toxicity related to ICPIs are discussed elsewhere. (See "Overview of toxicities associated with immune checkpoint inhibitors", section on 'Kidney'.)

Infections — Multiple organisms have been associated with AIN

including *Legionella*, *Leptospira*, cytomegalovirus (CMV), *Streptococcus*, *Mycobacterium tuberculosis*, *Corynebacterium diphtheriae*, Epstein-Barr virus (EBV), *Yersinia*, polyomavirus, *Enterococcus*, *Escherichia coli*, adenovirus, *Candida*, and others [10,13,41-43]. A histologic variant of AIN that is characterized by granuloma formation has been associated with *Mycobacterium*, fungi (histoplasmosis, coccidioidomycosis), bacteria (*Brucella*, *Chlamydia*, *Francisella*), spirochetes (*Treponema*), and parasites (*Leishmania*, *Toxoplasma*) [44]. However, the most common etiology of granulomatous interstitial nephritis in westernized countries is medication-related disease [45]. (See 'Histology' below.)

Initial reports suggested that organisms such as *Legionella*, *Leptospira*, CMV, and *Streptococcus* primarily invaded organs remote from the kidney and exerted an inflammatory response in the kidney without invading the kidney [42,43]. However, more recent reports describe the identification of organism-specific antigens or DNA in kidney proximal tubule cells of patients with AIN [41,46-48].

Drug-induced AIN is also relatively common among HIV-infected patients, although infections and immunologic syndromes associated with HIV infection can also induce AIN [49,50].

AIN has rarely been reported in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus infection. With infection, the AIN may have been related to medications rather than the viral infection itself [51,52]. AIN has also been reported after vaccination for SARS CoV-2 although proof of the vaccination as the etiologic stimulus is unproven [53].

Associated with systemic disease — Numerous systemic disorders have been associated with AIN. These primarily include SLE, sarcoidosis, and Sjögren's disease.

In a series of 133 patients with biopsy-proven AIN, of autoimmune etiologies, sarcoidosis was the most common [13]. (See "Kidney disease in primary Sjögren's disease" and "Kidney disease in sarcoidosis" and "Lupus nephritis: Diagnosis and classification", section on 'Tubulointerstitial lesions'.)

Patients with SLE and those with granulomatosis with polyangiitis often have interstitial nephritis accompanying the characteristic glomerular disease and may rarely present with AIN, even in the absence of glomerular disease.

Less common causes of AIN include IgG4-related disease [54,55] and hypocomplementemic tubulointerstitial nephritis [56-58]. IgG4-related disease is a systemic disorder characterized by the infiltration of multiple organs by a lymphoplasmacytic infiltrate that is rich in IgG4-positive plasma cells, resulting in diverse clinical manifestations, including autoimmune pancreatitis, enlarged lacrimal and salivary glands and periorbital tissue, and tubulointerstitial nephritis [54,59-65]. (See "Clinical manifestations and diagnosis of IgG4-related disease".)

Rare causes of AIN include antitubular basement membrane (TBM) antibodies [66-68], interstitial infiltration by immunoglobulin M (IgM)-positive plasma cells [69], and myelodysplastic syndrome [70]. In anti-TBM mediated AIN, anti-TBM antibodies lead to linear staining with immunoglobulin along the TBMs on immunofluorescence microscopy [66-68,71]. This can occur in the presence or absence of concurrent anti-glomerular basement membrane antibodies [66,67] and has been described in patients with membranous nephropathy [71] (see "Membranous nephropathy: Pathogenesis and etiology" and "Anti-GBM (Goodpasture) disease: Pathogenesis, clinical manifestations, and diagnosis", section on 'Kidney biopsy'). IgM plasma cell-mediated AIN is characterized by diffuse interstitial infiltration by IgM-positive plasma cells [69]. The clinical findings include a mild-to-moderate kidney function impairment and a high prevalence of distal renal tubular acidosis, Fanconi syndrome, and antimitochondrial antibodies. Serum IgM levels are markedly elevated. Corticosteroid treatment may lead to kidney function improvement in some patients.

Tubulointerstitial nephritis and uveitis (TINU) syndrome — Some patients with interstitial nephritis have the TINU syndrome. Patients present with interstitial nephritis and uveitis and occasionally with systemic findings including fever, weight loss, fatigue, malaise, anorexia, asthenia, abdominal and flank pain, arthralgias, myalgias, headache, polyuria, and/or nocturia. The TINU syndrome is discussed elsewhere.

(See "Tubulointerstitial nephritis and uveitis (TINU syndrome)".)

Older patients — There may be differences in the distribution of underlying causes of AIN among older and younger patients. In one review, patients 65 years and older were more likely to have drug-induced AIN compared with patients aged 18 to 64 years (87 versus 64 percent), and less likely to have AIN related to autoimmune or systemic diseases (7 versus 27 percent) [72]. There is no known biologic reason for this predilection, which is most likely related to polypharmacy in older individuals. The most common causative agents among older patients were penicillin and omeprazole.

A rare type of AIN in older patients is antibrush border antibody (ABBA) disease, which is caused by circulating antibodies reactive with megalin, an antigen present in the proximal tubule [73-75]. Most patients are elderly men who present with AKI and subnephrotic proteinuria. Concurrent pathologies are frequently identified (eg, diverse

glomerular and systemic diseases, malignancies, monoclonal paraproteinemia). Renal biopsy shows IgG staining along tubular basement membranes as a distinctive feature. The prognosis is poor, although some cases respond to immunosuppression.

EPIDEMIOLOGY

AIN is demonstrated in 1 to 3 percent of all kidney biopsies [76,77]. When analysis is restricted to biopsies performed in the setting of acute kidney injury (AKI), the percentage rises to approximately 13 to 19 percent [77,78].

Some studies suggest that the incidence of AIN is increasing, particularly among older subjects [13,72,77]. The reasons for this change are complex and difficult to assess but may include an aging population base, increasing polypharmacy (including nonsteroidal antiinflammatory drugs [NSAIDs] and proton pump inhibitors [PPIs]) in older people, and an increasingly less restrictive policy of kidney biopsies in older patients with AKI. The true incidence of AIN may also be underestimated for the following reasons [26]:

- A confirmatory kidney biopsy is often not done in older and frail patients; empirical treatment is often preferred.
- The prevalence of AIN caused by PPIs, 5-aminosalicylates, and NSAIDs and often without obvious associated symptoms is increasing [26]. Skin rash and eosinophilia are significantly less common with these drugs than in antibiotic-induced AIN. (See 'Clinical manifestations' below.)

CLINICAL FEATURES

Clinical manifestations — With AIN from any cause, patients may present with nonspecific signs and symptoms of acute kidney dysfunction. These may include the acute or subacute onset of nausea, vomiting, and malaise. However, many patients are asymptomatic [10]. Patients may be oliguric or nonoliguric; in a retrospective study that included 60 cases of AIN (92 percent of which were drug induced, with the remainder idiopathic), oliguria was present among 51 percent [11]. Gross hematuria occurs in approximately 5 percent of individuals [11].

Patients usually do not have significant proteinuria, and nephrotic syndrome occurs in <1 percent of patients with AIN [11]. An exception occurs among patients who have nonsteroidal antiinflammatory drug (NSAID)-induced AIN, which may occur concurrently with NSAID-induced membranous nephropathy or minimal change disease.

(See 'NSAID-induced AIN and nephrotic syndrome' below and 'Membranous nephropathy: Pathogenesis and etiology', section on 'Drugs'.)

Patients may present with symptoms related to the cause of the AIN. Classically, patients with drug-induced AIN were reported to have symptoms and/or signs of an allergic-type reaction, including rash, fever, and eosinophilia [79]. However, in a more recent review of three series that totaled 128 patients with AIN (of whom 70 percent had drug-induced disease), these findings of a typical allergic response were relatively less common at presentation [9]:

- Rash – 15 percent
- Fever – 27 percent

- Eosinophilia – 23 percent
- Triad of rash, fever, and eosinophilia – 10 percent

A similar incidence of findings was reported in two retrospective series, which collected a total of 121 patients [80,81]. Rash, fever, eosinophilia, and the triad were observed in 22, 36, 35, and 11 percent, respectively [11]. Arthralgias were observed in 45 percent of the patients [11].

Thus, the originally described classic triad is less commonly observed than initially reported. This is probably due to the absence of cases of methicillin-induced AIN and (perhaps) the increased inclusion of cases not directly resulting from an allergic response [10]. In addition, some agents, such as NSAIDs and proton pump inhibitors (PPIs), are less commonly associated with fever, rash, and eosinophilia compared with other agents [81,82].

There is no typical range of time of onset for medication-induced AIN. The onset of drug-induced AIN following drug exposure may range from three to five days (as occurs with a second exposure to an offending drug), to as long as several weeks, to many months (as occurs following a first exposure to an offending drug) [2,3]. However, the latent period from initial drug exposure may be as short as one day with rifampin [3] or as long as 18 months with an NSAID [82].

Patients who have AIN that is not related to a drug may have symptoms related to an associated infection or systemic condition such as systemic lupus erythematosus (SLE), sarcoidosis, the tubulointerstitial nephritis with uveitis (TINU) syndrome, and Sjögren's disease. (See "Tubulointerstitial nephritis and uveitis (TINU syndrome)" and "Kidney disease in primary Sjögren's disease" and "Kidney disease in sarcoidosis" and "Lupus nephritis: Diagnosis and classification", section on 'Tubulointerstitial lesions'.)

Patients with immunoglobulin G4 (IgG4)-related interstitial nephritis may have extrarenal signs and symptoms. In a series of 23 patients, nonspecific symptoms such as fever, arthralgias, skin lesions, and edema were present in three, five, one, and two patients, respectively [63]. Overall, 96 percent of patients with IgG4-related AIN had extrarenal lesions, including sialadenitis in 19 (82 percent), lymphadenopathy in 10 (44 percent), autoimmune pancreatitis in 9 (39 percent), dacryoadenitis in 7 (30 percent), and lung lesions (interstitial pneumonia and nodular lesions) in 6 (26 percent) [63]. In another study that included 118 patients with IgG4-related interstitial nephritis, extrarenal involvement by IgG4-related disease was present in 79 percent [83]. The most common extrarenal organs/tissues involved were the pancreas (40 percent), liver/biliary tract (18 percent), salivary glands (17 percent), lung (16 percent), and retroperitoneum (retroperitoneal fibrosis; 9 percent).

Laboratory and radiographic findings — In general, patients with AIN present with some combination of the following laboratory findings, with some variation based upon the underlying cause [2-4,9,80]:

- Increased plasma creatinine – Virtually all patients have a rise in the plasma creatinine concentration on presentation [80,81]. If AIN is drug induced, the increase in creatinine is temporally related to administration of the offending drug. Acute kidney injury (AKI) may be severe; in two retrospective series, among 121 patients who presented with AIN, 40 percent required dialysis [80,81].
- Eosinophilia and eosinophiluria – Although eosinophilia (defined by an absolute blood eosinophil count of ≥ 500 eosinophils/microL) is only found in 25 to 35

percent of AIN cases [9,11,80,81], its finding in a patient with AKI with no other apparent cause should raise the suspicion of drug-induced AIN. Eosinophiluria, defined by eosinophils that account for more than 1 percent of urinary white cells by Hansel stain [5,84], has been associated with AIN [85]. However, urinary eosinophils are not useful in distinguishing AIN from other causes of AKI, and the absence of eosinophiluria does not exclude the possibility of AIN. The lack of clinical utility of eosinophils in diagnosing AIN was best shown in a retrospective study that correlated urinary eosinophils with biopsy-proven AIN [86]. Five-hundred sixty-six patients had both a kidney biopsy and a test for urinary eosinophils performed for AKI. Among 179 patients who had a positive test for urinary eosinophils (defined as ≥ 1 percent of urinary white cells), only 28 had AIN on biopsy. Conversely, among 387 patients who had a negative test for eosinophils, 63 had biopsy-proven AIN. In this study, urinary eosinophils were found in multiple other kidney diseases, including acute tubular necrosis and crescentic and proliferative glomerulonephritis, and their presence did not alter the pretest probability of AIN on biopsy.

Some reports [81,82], though not all [86], have suggested that eosinophilia and eosinophiluria are less common in AIN induced by NSAIDs compared with other drugs.

- **A characteristic urine sediment** – The urine sediment usually reveals white cells, red cells, and white cell casts (picture 1A-B). Red blood cell casts, which are typically seen in glomerulonephritis, have also been described in AIN, although this is rare [87]. Some patients will, however, have no urinary sediment findings or isolated microhematuria and leukocyturia. The absence of urinary findings does not exclude a diagnosis of AIN.

- **A variable degree of proteinuria** – Proteinuria can range from none or minimal to >1 g/day. In two retrospective series that included a total of 121 patients, the mean and median protein excretions were 0.9 ± 1.1 g/day (range 0 to 6 g/day) and 0.70 g/day (interquartile range 0.39 to 1.0 g/day), respectively [80,81]. Older individuals may be more likely to have significant proteinuria [78].

Occasional patients will have nephrotic-range proteinuria [2,3,11]. Concurrent nephrotic syndrome due to minimal change disease or membranous nephropathy can rarely be seen with NSAIDs and, in selected cases, induced by ampicillin, rifampin, interferon, or ranitidine [11,24,82,88,89]. In one study cited above, however, although proteinuria was significantly higher among NSAID-induced AIN as compared with other types of drug-induced AIN, nephrotic-range proteinuria was rare [81]. In addition, although these and other drugs may induce heavy proteinuria [14], an underlying disease (such as diabetic nephropathy or glomerulonephritis due to bacterial endocarditis) may be responsible for at least part of the proteinuria in some patients.

- **Evidence of tubulointerstitial damage** – Signs of tubulointerstitial damage, such as the Fanconi syndrome and renal tubular acidosis, may be present but rarely dominate the clinical picture [25].

- **High fractional sodium excretion** – The fractional excretion of sodium (FENa) may be >1 percent, which is in part indicative of tubular damage [2]. Calculators for the FENa are available using either standard units (calculator 1) or SI units (calculator

2) (see "Fractional excretion of sodium, urea, and other molecules in acute kidney injury", section on 'Approach to using fena in acute kidney injury'). However, lower values may be seen, particularly in patients who are nonoliguric and have less severe kidney failure [90,91].

- Radiographic findings – There are no radiographic findings that are diagnostic for AIN. Radiographic findings, including marked enlargement of kidneys with low-attenuation lesions, may be seen among patients with IgG4-related AIN [55].

Microbiologic features unique to different culprit organisms are presented separately. (See appropriate topic reviews.)

IgG4-related disease and hypocomplementemic interstitial nephritis — In addition to the above findings, patients with immunoglobulin G4 (IgG4)-related disease or hypocomplementemic interstitial nephritis usually have elevated serum total IgG and/or IgG4 levels or hypergammaglobulinemia and may have low serum complement concentrations [63,92]. In one series of IgG4-related tubulointerstitial nephritis, among 23 patients, complement C3, C4, or both were reduced in 16 [63]. In another study that included 118 patients with IgG4-related interstitial nephritis, elevated IgG4 levels were present in approximately 80 percent and low C3 or C4 was present in approximately 60 percent of patients who had available laboratories [83].

DIAGNOSIS

AIN should be suspected in a patient who presents with an elevated serum creatinine and a urinalysis that shows white cells, white cell casts, and, in some cases, eosinophiluria. Red blood cells and, rarely, red blood cell casts can be also observed [93,94], although gross hematuria is distinctly unusual. Drug-induced AIN should be suspected when the onset of characteristic laboratory findings is temporally related to the initiation of a new drug, particularly one that has been previously reported to cause AIN. However, occasional patients have a bland sediment with few cells or casts [18]. Thus, a relatively normal urinalysis should not exclude the diagnosis.

A definitive diagnosis of AIN is made by kidney biopsy. It is often considered unnecessary to make a definitive diagnosis, such as among patients who have clearly documented onset of kidney failure after initiation of a common culprit drug and who improve immediately upon stopping the offending agent.

We suggest a kidney biopsy for the following patients who are suspected of having AIN:

- Patients who have a characteristic urinalysis for AIN but are not being treated with a drug known to cause AIN.
- Patients who are being treated with a drug known to cause AIN but do not have a characteristic urinalysis. Some of the drugs that cause AIN can also produce other forms of acute kidney injury (AKI). As an example, nonsteroidal antiinflammatory drugs (NSAIDs) can exacerbate prekidney disease by inhibiting the production of vasodilator prostaglandins [82]. (See "NSAIDs: Acute kidney injury".)

- Patients who are being considered for treatment with glucocorticoids for AIN (usually drug induced). Among selected patients (such as those at high risk of complications of a biopsy or who do not wish to undergo a biopsy), glucocorticoids may be initiated without first obtaining a kidney biopsy. However, among patients who do not improve after the first five to seven days of empiric glucocorticoid therapy, those without contraindications should have a biopsy in order to exclude other diagnoses or severe interstitial fibrosis. (See "The kidney biopsy", section on 'Contraindications' and 'Treatment of acute interstitial nephritis'.)
- Patients with putative drug-related AIN who are not treated with glucocorticoids initially and do not have a recovery following cessation of drug therapy [2,80]. We typically perform a kidney biopsy approximately two weeks after cessation of the offending drug if there has been no improvement in the kidney function over that time. However, clinicians wait a variable amount of time to allow for recovery before performing a biopsy. Some wait for three to four days, whereas others wait until the patient is approaching the need for kidney replacement therapy.
- Patients who present with advanced kidney failure, providing the onset of kidney failure is known to be relatively recent (ie, within three months).
- Patients with any features (such as high-grade proteinuria) that cause the diagnosis of AIN to be uncertain.

Patients who have a characteristic urinalysis for AIN but do not have an elevated creatinine may also be considered for biopsy, but such patients rarely come to medical attention since the urinalysis is usually only performed after the detection of an increased serum creatinine. Moreover, it is usually simpler and safer just to remove potential offending medications in such cases.

Prediction models have been created to diagnose AIN from the electronic medical record [95,96]. However, the role of such models in clinical care is currently unclear.

The approach to the treatment of patients diagnosed with AIN, tubulointerstitial nephritis with uveitis (TINU), and kidney sarcoidosis is presented separately.

- (See "Treatment of acute interstitial nephritis".)
- (See "Kidney disease in sarcoidosis".)
- (See "Tubulointerstitial nephritis and uveitis (TINU syndrome)".)

Histology — The major histologic changes are interstitial edema and a marked interstitial infiltrate consisting primarily of T lymphocytes and monocytes (picture 2A-E) [2,9]. Eosinophils, plasma cells, and neutrophils also may be found. The classic lesion of "tubulitis" is found when inflammatory cells invade the tubular basement membrane (TBM).

Some histologic features may suggest particular variants of AIN. As an example, granuloma formation is particularly characteristic of sarcoidosis, although it may be seen in any form of AIN [97]. In some series, granuloma formation also suggests a greater likelihood of infection-induced AIN compared with AIN without granulomas. In a review of 40 biopsies of patients with granulomatous kidney disease (including 37 patients with interstitial nephritis, two with associated pauci-immune crescentic glomerulonephritis, and one with vasculitis), sarcoidosis was present in 20 patients (50

percent) and drug-induced and *Mycobacterium* infection present in seven (18 percent) and five (13 percent), respectively [98]. However, in a number of other series, medication-induced interstitial nephritis was the leading cause of granulomatous interstitial nephritis, equaling or exceeding sarcoidosis in all.

Infection is a more likely etiology in areas where infections associated with granulomatous disease are more common than in westernized countries [45]. As described above, other infections that have been associated with granulomatous AIN include fungi (histoplasmosis, coccidioidomycosis), bacteria (*Brucella*, *Chlamydia*, *Francisella*), spirochetes (*Treponema*), and parasites (*Leishmania*, *Toxoplasma*) [44]. (See 'Infections' above.)

Characteristic features that suggest immunoglobulin G4 (IgG4)-related disease include a plasma cell-rich interstitial infiltrate, storiform interstitial fibrosis, an increase in IgG4-positive plasma cells, and the presence of TBM immune complex deposits [55,83]. A small proportion of patients with IgG4-related interstitial nephritis also have membranous nephropathy (MN): in a study of 118 patients with IgG4-related interstitial nephritis, 13 patients (11 percent) were found to have concomitant MN [83].

Patients with interstitial nephritis related to lupus usually have concurrent glomerular lesions. (See "Lupus nephritis: Diagnosis and classification", section on 'Clinical features' and "Lupus nephritis: Diagnosis and classification", section on 'Histopathologic classification of LN' and "Lupus nephritis: Diagnosis and classification", section on 'Other forms of lupus kidney disease'.)

Differential diagnosis — The differential diagnosis of AIN includes all other causes of AKI. The diagnostic approach to the patient with AKI from any cause is presented elsewhere. (See "Diagnostic approach to adult patients with subacute kidney injury in an outpatient setting".)

In general, the urinary findings will help distinguish AIN from other causes of AKI. The urinalysis, for example, typically shows granular and epithelial cell casts and free epithelial cells in acute tubular necrosis; red cell casts, as well as red and white cells in acute glomerulonephritis; and few, if any, abnormalities in hemodynamic AKI or obstruction.

Among patients with a predominance of white blood cells and white blood cell casts, renal atheroemboli should be considered, particularly among older patients [99]. Similarly to AIN, renal atheroemboli may present with eosinophiluria, eosinophilia, and skin lesions. However, atheroemboli are more commonly associated with a reticular pattern (livedo reticularis) and digital infarcts, whereas AIN is associated with a characteristic rash that is diffuse and maculopapular. The history may also distinguish between AIN and renal atheroemboli. Many atheroemboli occur in the setting of atherosclerotic cardiovascular disease and are preceded by an endovascular procedure. (See "Clinical presentation, evaluation, and treatment of renal atheroemboli" and "Clinical presentation, evaluation, and treatment of renal atheroemboli", section on 'Risk factors'.)

Among patients who have a completely negative sediment, as in all patients with AKI of obscure origin, obstruction should be considered as part of the differential diagnosis. Imaging studies (usually an ultrasound) generally exclude the presence of obstruction, except in rare cases when the diagnosis of AKI is made within the first two to three days

(see "Clinical manifestations and diagnosis of urinary tract obstruction (UTO) and hydronephrosis"). In all patients, imaging should be done prior to kidney biopsy. Novel noninvasive biomarkers such as tumor necrosis factor- α , interleukin-9, the urine ratio of retinol-binding protein-to-creatinine, and the urinary protein CXCL9 may help distinguish AIN from other diagnoses [100-102]. However, the role of such biomarkers in clinical care is currently unclear.

ESTABLISHING THE CAUSE

Once a diagnosis of AIN is made by biopsy, the underlying cause should be determined. As discussed above, the vast majority of cases of AIN are caused by a drug. A careful review of medications, including the timing of initiation in relation to the onset of acute kidney injury (AKI), may reveal the likely culprit agent.

Less commonly, a drug is not identified or suspected. Among such patients, a histologic diagnosis of AIN should provoke a search for underlying infection and systemic disorders including systemic lupus erythematosus (SLE), sarcoidosis, Sjögren's disease, tubulointerstitial nephritis and uveitis (TINU) syndrome, IgG4 disease, and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis.

In some cases, histologic features may suggest the underlying disease that is associated with AIN. As an example, granulomas are more likely to be seen in patients with sarcoidosis than in other forms of AIN. Additionally, AIN related to SLE may be accompanied by characteristic glomerular lesions. Immunoglobulin G4 (IgG4)-related disease may be suggested by the presence of tubular basement membrane (TBM) immune complex deposits and an increase in immunoglobulin G4 (IgG4)-positive plasma cells in the interstitium [55]. However, testing for IgG-4 specific plasma cells is not routinely performed at most centers.

Such histologic features, although often suggestive, are not diagnostic, and, in general, the etiology of non-drug-related AIN must be established by means other than the kidney biopsy. Among patients who have AIN that is not believed to be related to a drug, we perform the following tests:

- Chest radiograph to evaluate for sarcoidosis, tuberculosis, and other infections. Among patients in whom the chest radiograph is nondiagnostic, a high-resolution chest computed tomography (CT) should be obtained to evaluate for sarcoidosis.
- Serum levels of angiotensin-converting enzyme (ACE) and measurement of serum calcium and urinary calcium excretion to evaluate for sarcoidosis.
- Serum QuantiFERON gold test or a purified protein derivative (PPD) to exclude tuberculosis, particularly in granulomatous AIN.
- Serologic tests, in select cases, to exclude histoplasmosis, coccidioidomycosis, toxoplasmosis, and Epstein-Barr virus (EBV). Urinary antigen test to exclude *Legionella* infection and urine culture to exclude leptospirosis.
- ANCA to exclude ANCA-associated vasculitides.

- Antinuclear antibody (ANA) and double-stranded DNA (dsDNA) to exclude SLE.
- C3 and C4 to evaluate for SLE and IgG4-related disease and hypocomplementemic AIN. These tests, however, neither diagnose nor exclude these disorders.
- Anti-Ro/SSA, anti-La/SSb antibodies, C-reactive protein, and rheumatoid factor to exclude Sjögren's disease.
- Serum protein electrophoresis.
- Slit lamp examination in patients with eye pain or redness to evaluate for tubulointerstitial nephritis and uveitis (TINU syndrome).
- The diagnostic evaluation of a particular infection-related AIN should be guided by extrarenal clinical manifestations.

NSAID-INDUCED AIN AND NEPHROTIC SYNDROME

Nonsteroidal antiinflammatory drugs (NSAIDs) may cause AIN with an interstitial infiltrate composed primarily of T lymphocytes, and with the nephrotic syndrome due to minimal change disease or membranous nephropathy [82,103-105].

This disorder is most likely to occur with fenoprofen but probably can be induced by any nonselective NSAID. There have also been case reports of selective cyclooxygenase (COX)-2 inhibitors also being associated with this pattern of injury [21,106,107].

How NSAIDs produce AIN and nephrotic syndrome are not known; it is possible that COX inhibition by the NSAID results in the preferential conversion of arachidonic acid to leukotrienes, which can then activate helper T cells.

Affected patients typically present with hematuria, pyuria, white cell casts, proteinuria, and an acute rise in the plasma creatinine concentration. The full picture of an allergic reaction (fever, rash, eosinophilia, and eosinophiluria) is typically absent, but one or more of these findings may be present. Spontaneous recovery generally occurs within weeks to a few months after therapy is discontinued [82,103]. All NSAIDs should be terminated in patients suspected of having NSAID-induced AIN. Since topically administered NSAIDs can be systemically absorbed, such therapy should also be terminated [108].

There is no definitive evidence that corticosteroid therapy is beneficial in this setting. However, a course of prednisone may be considered in patients whose kidney failure persists more than one to two weeks after the NSAID has been discontinued [2].

(See "Treatment of acute interstitial nephritis".)

Such patients should avoid the subsequent administration of NSAIDs. Relapse may occur with rechallenge [109].

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: Acute kidney injury in adults".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Acute interstitial nephritis (The Basics)")

SUMMARY AND RECOMMENDATIONS

- Overview** – Acute interstitial nephritis (AIN) is a kidney lesion that causes a decline in kidney function and is characterized by an inflammatory infiltrate in the kidney interstitium. Drugs, particularly antibiotics, are the most common cause of AIN. Other causes include autoimmune disorders, infections, sarcoidosis, and tubulointerstitial nephritis with uveitis (TINU) syndrome. (See 'Introduction' above.)

- Etiology**

- Drugs** – Drugs that most commonly cause AIN are nonsteroidal antiinflammatory drugs (NSAIDs, including selective cyclooxygenase [COX]-2 inhibitors), penicillins and cephalosporins, rifampin, antimicrobial sulfonamides, ciprofloxacin and other quinolones, diuretics, cimetidine, allopurinol, proton pump inhibitors (PPIs), 5-aminosalicylates (eg, mesalamine), and checkpoint-inhibiting monoclonal antibodies. Many other drugs can occasionally cause AIN. (See 'Drugs' above.)

- Infections** – Infections that have been associated with AIN include *Legionella*, *Leptospira*, cytomegalovirus (CMV), and *Streptococcus*. Other, less commonly associated organisms include *Corynebacterium diphtheriae*, Epstein-Barr virus (EBV), *Yersinia*, and polyomavirus. *Mycobacterium* infection is associated with a granulomatous variant of AIN. (See 'Infections' above.)

- Autoimmune disorders** – Autoimmune disorders that have been associated with AIN include sarcoidosis, Sjögren's disease, systemic lupus erythematosus (SLE), and granulomatosis with polyangiitis. Less common causes of AIN are immunoglobulin G4 (IgG4)-related disease, anti-tubular basement membrane

(TBM) antibodies, hypocomplementemic tubulointerstitial nephritis, and the TINU syndrome. (See 'Associated with systemic disease' above.)

•**Clinical features**

•**Clinical manifestations** – Patients with AIN present with nonspecific signs and symptoms associated with acute kidney injury (AKI). Signs and symptoms of an allergic-type reaction may be present, including rash, fever, and eosinophilia, although only 10 percent of patients have the full triad of rash, fever, and eosinophilia. (See 'Clinical manifestations' above.)

•**Laboratory findings** – Patients generally present with a rise in the plasma creatinine concentration, which (if drug induced) is temporally related to administration of the offending drug. Urine sediment usually reveals white cells, red cells, and white cell casts. Urinary eosinophils may be present but lack the specificity and sensitivity to either exclude or diagnose AIN. Protein excretion is usually only mildly or moderately increased. (See 'Laboratory and radiographic findings' above.)

•**Diagnosis** – AIN should be suspected in a patient who presents with an elevated serum creatinine and a urinalysis that shows white cells, white cell casts, and, in some cases, eosinophiluria. Drug-induced AIN should be suspected when the onset of characteristic laboratory findings are temporally related to the initiation of a new drug, particularly one that has been previously reported to cause AIN. A definitive diagnosis of AIN is made by kidney biopsy. Selected patients with suspected AIN will benefit from kidney biopsy. (See 'Diagnosis' above.)

•**Establishing the cause** – Patients who have a histologic diagnosis of AIN and are not on a drug known to cause AIN should be evaluated for another underlying etiology. (See 'Establishing the cause' above.)

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Clinicopathological Characteristics and Kidney Outcomes in Biopsy-Confirmed Acute Interstitial Nephritis



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Introduction: Acute interstitial nephritis (AIN) is a significant cause of acute kidney injury, with varying etiologies and outcomes. This study aimed to examine the causes, clinical characteristics, management, and kidney outcomes in patients with biopsy-confirmed AIN.

Methods: A retrospective review was conducted on 166 patients diagnosed with AIN through kidney biopsy at Mayo Clinic between 2012 and 2023. Demographic, clinical, laboratory, and pathological data were collected. The primary outcome was kidney function recovery within the first 6 months. Statistical analyses included univariable and multivariable logistic regression, Kaplan-Meier survival analysis, and Cox proportional hazards modeling.

Results: Medications were the primary cause of AIN (67%), followed by autoimmune diseases (20%) and infections (6%). Within 6 months, 76% of patients achieved kidney recovery. Multivariable analysis indicated that moderate to severe interstitial fibrosis and tubular atrophy (IFTA) and dialysis requirement were associated with nonrecovery, whereas a prebiopsy diagnosis of AIN was positively associated with kidney recovery. Drug-related AIN had higher recovery rates compared to all other causes (81% vs. 66%, $P = 0.04$), and moderate to severe IFTA and dialysis need remained significant predictors of decreased recovery. Steroid therapy, used in 81% of patients, did not significantly influence kidney recovery in the overall cohort or in drug-induced AIN.

Conclusion: This study provides insights into the characteristics and outcomes of biopsy-confirmed AIN. IFTA and dialysis requirement were significant factors associated with worse kidney outcomes. These findings may help inform clinical management and prognostication in patients with AIN.

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KEYWORDS: acute interstitial nephritis; clinicopathological features; etiology; kidney outcomes; steroid therapy

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AIN is a significant and potentially reversible cause of acute kidney injury, particularly among hospitalized individuals, accounting for 15% to 27% of cases.^{1,2} Whereas some patients experience full recovery of kidney function, a considerable proportion, ranging from 30% to 70% may not achieve complete recovery and instead progress to chronic kidney disease (CKD).³ Studies show that individuals with biopsy-confirmed AIN have a 5% to 7% risk of advancing to end-stage kidney disease (ESKD), requiring dialysis.^{4,5}

The etiology of AIN is diverse, with drugs implicated in over two-thirds (70%–75%) of cases, followed

by autoimmune diseases (10%–20%), and infections (4%–10%).^{6,7} Consequently, the clinical, laboratory, and histopathological presentations of AIN can vary significantly.⁸ Treatment typically involves the cessation of any offending agents and the administration of immunosuppressive therapy, mainly steroids, although the efficacy of this regimen is currently under debate.^{1,3-5,9-11} The clinical management of patients with AIN presents significant challenges due to its frequently uncharacteristic and atypical manifestations in many cases. It remains unclear whether specific clinical and laboratory characteristics can predict response to steroids and improved kidney outcomes. An in-depth exploration of the clinicopathological attributes, including the effects of steroid therapy and kidney outcomes, is critically needed.

In this retrospective analysis, we explored the etiology, clinical presentation, histopathological features,

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laboratory findings, and steroid treatment in a cohort of 166 patients diagnosed with biopsy-confirmed AIN over the past 10 years. Our aim was to pinpoint prognostic indicators associated with kidney outcomes.

METHODS

Study Population

This study was approved by the Institutional Review Board of Mayo Clinic. We conducted a retrospective chart review of patients diagnosed with biopsy-confirmed AIN at Mayo Clinic between January 1, 2012, and December 31, 2023. We used Mayo Data Explorer to search and identify eligible patients in Renal Pathology Laboratory database. Subsequently, we manually reviewed kidney pathology reports to confirm AIN diagnosis. The study excluded patients aged <18 years, those diagnosed with glomerulonephritis or primary vascular disease, and those with transplant biopsies.

Data Collection

We reviewed and collected demographic, clinical, laboratory, and pathological data. A pathologic diagnosis of AIN is based on the presence of prominent interstitial inflammation in the nonfibrotic cortex and tubulitis.¹ Biopsy time was established as the baseline. Leukocytosis was defined by a leukocyte count greater than $10.5 \times 10^9/L$, eosinophilia was defined by an eosinophil count exceeding $0.5 \times 10^9/L$, and eosinophiluria was defined by more than 1% urine eosinophils. The estimated glomerular filtration rate was calculated using the CKD-Epidemiology Collaboration formula, expressed in ml/min per 1.73 m^2 .

Kidney Outcomes

The primary outcome assessed was the recovery of kidney function, determined by the available serum creatinine (sCr) measurement within the first 6 months. Complete recovery was achieved when the sCr level returns to within 25% of its baseline or to below 1.4 mg/dl if the baseline is unknown. Partial recovery was defined as a reduction in sCr by at least 50% from its peak, without returning to within 25% of the baseline. No recovery included cases that did not meet the criteria for complete or partial recovery or those remaining on kidney replacement therapy.

The secondary outcome, evaluated at the 6-month follow-up, included normal kidney function, progression to CKD, and ESKD. Normal kidney function was characterized by a final sCr level < 1.4 mg/dl, progressive CKD by an sCr level $\geq 1.4 \text{ mg/dl}$, and ESKD if the patient continued on dialysis therapy or had received a kidney transplant. The definitions for kidney recovery and secondary kidney outcomes in this

study aligned with those used in our institution's previous study, which covered the period from 1993 to 2011,¹ to facilitate a comparison of AIN outcomes between the 2 timeframes.

Statistical Analysis

Data were expressed as either mean $\pm$ SD or median with interquartile range for continuous variables, and as counts with percentages for categorical variables. Categorical characteristics between groups were compared using either Fisher exact test or chi-square test. For continuous variables, the *t* test or Wilcoxon rank sum test was employed for comparisons between 2 groups, whereas 1-way ANOVA was used to assess differences across multiple groups. Kidney recovery was analyzed using Kaplan-Meier survival analysis. Univariable and multivariable logistic regression analyses were conducted to identify factors associated with kidney recovery. In addition, a Cox proportional hazards model was employed to assess the association between steroid treatment and kidney recovery. Results from the logistic and Cox models were presented as odds ratios and hazard ratios with 95% confidence intervals (CI), respectively. Statistical significance was set at $P < 0.05$. Statistical analyses were carried out using JMP Pro software, version 14.3.0 (SAS Institute Inc., NC).

RESULTS

Comparative clinical characteristics of patients achieving versus those not achieving kidney recovery within 6 months.

A total of 166 patients with AIN were identified in this study. In Table 1, we display the demographic and clinical data for the entire cohort. The average age was 59 ± 17 years, with approximately half being male. The incidence of rash, fever, and oliguria was notably low within the cohort, affecting less than 16% of patients. Only 2 patients exhibited the triad of these symptoms, representing 1.2% of the study group.

Within the cohort, a significant portion of the patients (76%; 126 out of 166) experienced kidney recovery either complete ($n = 85$) or partial ($n = 25$), with a median recovery time of 1.7 months. Approximately 18% of patients in the nonrecovery group had an unknown cause of AIN, a proportion significantly larger than the 6% observed in the recovery group ($P = 0.05$). The baseline sCr did not differ between those who recovered and those who did not (1.2 ± 0.5 vs. 1.4 ± 0.7 , $P = 0.58$). Compared to patients with recovery, those without recovery had a higher incidence of moderate to severe IFTA (59% vs. 22%, $P < 0.001$) and global glomerulosclerosis (44% vs. 17%, $P = 0.003$), presence of granulomas (33% vs. 17%, $P = 0.04$), and a need for dialysis (40% vs. 7%, $P < 0.001$); however,

Table 1. Clinical, laboratory, histopathological, and treatment comparisons in the entire acute interstitial nephritis cohort: recovery versus nonrecovery

Characteristics	All patients (N = 168)	Recovery (n = 126) ^a	Nonrecovery (n = 40)	P value
Age at the biopsy (yr)	58.6 ± 17.0	59.0 ± 16.7	56.4 ± 17.6	0.78
Male sex, n (%)	83 (49.7)	63 (50.0)	20 (50.0)	>0.99
White race, n (%) ^b	152 (93.2)	122 (97.6)	30 (79.0)	<0.001
BMI (kg/m ²)	29.6 ± 7.7	29.5 ± 7.0	29.5 ± 9.8	0.53
Comorbidities, n (%)	158 (95.2)	119 (94.4)	39 (97.5)	0.68
Prebiopsy AIN diagnosis, n (%)	130 (78.3)	106 (84.1)	24 (60.0)	0.003
Causes of AIN				
Drug-related, n (%)	111 (66.9)	90 (71.4)	21 (52.5)	0.03
Autoimmune-related, n (%)	33 (19.9)	27 (21.4)	6 (15.0)	0.49
Infection-related, n (%)	10 (6.0)	6 (4.9)	4 (10.0)	0.52
Unknown, n (%)	15 (9.0)	8 (6.4)	7 (17.5)	0.05
Other, n (%)	4 (2.4)	2 (1.6)	2 (5.0)	na
Multiple causes, n (%)	7 (4.2)	7 (5.6)	0	na
Clinical presentation				
Rash, n (%)	21 (12.7)	16 (12.7)	5 (12.5)	>0.99
Fever, n (%)	23 (13.9)	16 (12.7)	7 (17.5)	0.44
Oliguria, n (%)	27 (16.3)	16 (12.7)	11 (27.5)	0.046
Triad sign, n (%)	2 (1.2)	2 (1.6)	0	>0.99
CKD prior to biopsy, n (%)	59/161 (36.6)	41/123 (33.9)	18/38 (47.4)	0.13
Baseline sCr (mg/dl)	1.3 ± 0.5	1.2 ± 0.5	1.4 ± 0.7	0.58
Baseline sCr in CKD (mg/dl)	1.8 ± 0.6	1.7 ± 0.5	1.9 ± 0.7	0.31
Baseline eGFR in CKD (ml/min per 1.73 m ²)	42 (32–50)	42 (33–50)	26 (25–50)	0.34
Baseline sCr without CKD (mg/dl)	1.0 ± 0.2	1.0 ± 0.2	1.0 ± 0.12	>0.99
Baseline eGFR without CKD (ml/min per 1.73m ²)	78 (71–90)	78 (69–89)	79 (74–94)	0.43
Kidney size, n	137	103	34	0.23
Normal, n (%)	123 (89.8)	95 (92.2)	28 (82.4)	
Small, n (%)	4 (2.9)	2 (1.9)	2 (5.9)	
Large, n (%)	10 (7.3)	6 (5.8)	4 (11.8)	
AKI stage	165	126	39	0.78
Stage 1	33 (20.0)	26 (20.6)	7 (18.0)	
Stage 2	32 (19.4)	23 (18.3)	9 (23.1)	
Stage 3	100 (60.6)	77 (61.1)	23 (59.0)	
Kidney biopsy				
IFTA, n	163	125	39	<0.001
None, n (%)	44 (27.0)	41 (32.8)	3 (7.7)	
Mild, n (%)	69 (41.7)	56 (44.8)	13 (33.3)	
Moderate, n (%)	35 (21.5)	23 (18.4)	12 (30.8)	
Severe, n (%)	16 (9.8)	5 (4.0)	11 (28.2)	
Globally glomerulosclerosis, n	163	125	39	0.003
None, n (%)	77 (47.2)	64 (51.2)	14 (35.9)	
Mild, n (%)	48 (29.4)	40 (32.0)	8 (20.5)	
Moderate, n (%)	26 (16.0)	16 (12.8)	10 (25.6)	
Severe, n (%)	12 (7.4)	5 (4.0)	7 (18.0)	
Granuloma present, n (%)	34 (20.5)	21 (16.5)	13 (32.5)	0.04
Laboratory test				
sCr at biopsy (mg/dl)	3.0 (2.0–4.7)	2.9 (2.0–4.7)	3.1 (2.1–5.6)	0.21
Peak sCr (mg/dl)	3.8 (2.5–6.2)	3.8 (2.5–6.9)	4.4 (2.3–7.4)	0.43
Albumin at biopsy (g/dl)	3.7 ± 0.74	3.73 ± 0.76	3.62 ± 0.69	0.45
24h proteinuria at biopsy (g/24-h)	0.5 (0.2–0.9)	0.4 (0.2–0.9)	0.6 (0.2–2.2)	0.10
CRP at biopsy (mg/dl)	17.1 (5.0–61.3)	22.9 (5.9–68.4)	10.4 (2.9–15.4)	0.02
ESR at biopsy (mm/h)	48 (30–85)	49 (31–82)	35 (17–58)	0.33
Neutrophil count (x 10 ⁹ /L)	5.2 (3.5–7.0)	5.4 (3.6–7.1)	4.3 (2.8–6.7)	0.04
Lymphocytes count (x 10 ⁹ /L)	1.3 (0.9–1.8)	1.3 (1.0–1.8)	1.2 (0.7–1.7)	0.53
Leukocytosis, n (%)	31 (18.7)	27 (21.4)	4 (10.0)	0.16
Eosinophilia, n (%)	22/151 (14.6)	19/118 (16.1)	3/33 (9.1)	0.41
Urine WBC present, n (%)	135/163 (82.8)	105/125 (84.0)	30/38 (78.9)	0.47
Urine RBC present, n (%)	111/164 (67.7)	86 (68.3)	25/38 (65.8)	0.84
Urine WBC cast present, n (%)	5/163 (3.1)	4/125 (3.2)	1/38 (2.6)	>0.99

(Continued on following page)

Table 1. (Continued) Clinical, laboratory, histopathological, and treatment comparisons in the entire acute interstitial nephritis cohort: recovery versus nonrecovery

Characteristics	All patients (N = 166)	Recovery (n = 126) ^a	Nonrecovery (n = 40)	P value
Urine RBC cast present, n (%)	1/163 (0.6)	1/125 (0.8)	0	>0.99
Eosinophiluria, n (%)	13/102 (12.7)	10/72 (13.9)	3/30 (10.0)	0.75
Urine RTE cell present, n (%)	20/164 (12.2)	18 (14.3)	2/38 (5.3)	0.17
Urine RTE cast present, n (%)	3/162 (1.9)	3/124 (2.4)	0	>0.99
Urine granular cast present, n (%)	35/164 (21.3)	24 (19.1)	11/38 (29.0)	0.26
Treatment				
Steroid therapy, n (%)	134 (80.7)	104 (82.5)	30 (75.0)	0.36
Time to start steroid after biopsy (d)	2 (1–5)	2 (1–5)	2 (1–14)	0.26
Duration of steroids (weeks)	10 (6–24)	10 (6–24)	9 (5–23)	0.71
IV steroids given initially, n (%)	25/138 (18.1)	22/107 (20.6)	3/31 (9.7)	0.20
MMF, n (%)	8 (4.8)	7 (5.6)	1 (2.5)	0.68
Dialysis required, n (%)	25 (15.1)	9 (7.1)	16 (40.0)	<0.001
Death, n (%)	8 (4.8)	3 (2.4)	5 (12.5)	0.02
Kidney outcome				
Recovery within the first 6 mo				na
Complete recovery, n (%)	85 (51.2) ^c	na	na	
Partial recovery, n (%)	41 (24.7)	na	na	
No recovery, n (%)	40 (24.1)	na	na	
Time to recovery (mo)	na	1.7 (0.8, 3.1)	na	
Outcome at 6-mo follow-up, n	128 ^d	97	31	<0.0001
Normal kidney function, n (%)	50 (39.0) ^e	50 (51.6)	0	
Progressive CKD, n (%)	63 (49.2)	47 (48.5)	16 (51.6)	
ESKD, n (%)	15 (11.7)	0	15 (48.4)	

AIN, acute interstitial nephritis; AKI, acute kidney injury; BMI, body mass index; CKD, chronic kidney disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; ESR, erythrocyte sedimentation rate; ICIs, immune checkpoint inhibitors; IFTA, interstitial fibrosis and tubular atrophy; IQR, interquartile range; MMF, mycophenolate mofetil; na, not applicable; NSAIDs, non-steroidal anti-inflammatory drugs; PPIs, proton pump inhibitors; RTE, renal tubule epithelial; sCr, serum creatinine; WBC, white blood cell; RBC, red blood cell.

Results are presented as mean $\pm$ SD or median (IQR) for continuous variables and as n (%) for categorical variables.

^aThe recovery indicates either complete or partial recovery.

^bUnreleased in 2 patients did not achieve recovery.

^cPatients who achieved complete recovery had their sCr levels decrease from a peak of 4.5 ± 2.9 mg/dl (median 3.7 mg/dl, IQR: 2.4–5.6) to 1.4 ± 0.4 mg/dl, which was not statistically different from their baseline level of 1.3 ± 0.5 mg/dl ($P = 0.23$).

^dEight patients died, and 30 patients were lost to follow-up at the 6-month end point (26 from the recovery group and 4 from the nonrecovery group). Thus, there were 128 patients in total at the 6-month end point.

^eIn patients who reached normal kidney function, their sCr levels decreased from a peak of 4.7 ± 3.1 mg/dl (median 3.7 mg/dl, IQR: 2.3–6.0) to 1.1 ± 0.2 mg/dl, with no significant difference compared to their baseline value of 0.98 ± 0.24 mg/dl ($P = 0.36$).

they had lower levels of C-reactive protein (CRP; 10 mg/dl vs. 23 mg/dl, $P = 0.02$) and neutrophil counts ($4.3 \times 10^9/L$ vs. $5.4 \times 10^9/L$, $P = 0.04$). Among patients who achieved kidney recovery, 71% had drug-related AIN, compared to 53% in those who did not recover ($P = 0.03$). At the 6-month follow-up, kidney function normalized in half of the patients who achieved kidney recovery. In contrast, all patients who did not recover experienced either progressive CKD (52%) or progressed to ESKD (48%).

Causes of AIN

In Table 2, we outline the various causes of AIN. Medications emerged as the predominant cause, responsible for 67% of cases; with autoimmune diseases contributing to 20%; and infections contributing to 6%. In 9% of cases, the cause of AIN could not be determined. In addition, 4.2% of patients had multiple causes for their AIN, such as a combination of drug-related and autoimmune or infectious diseases. In the category of autoimmune-related AIN, Sjogren's

syndrome and sarcoidosis were the most common causes (33% and 21%, respectively). Among the infectious-related AIN, bacterial and fungal infections were the primary causes, accounting for 50% and 40% of these cases, respectively. Within the drug-related category, antibiotics were the most common cause, making up 36% of these cases, followed by proton pump inhibitors (PPIs) at 29%, immune checkpoint inhibitors (ICIs) at 18%, and nonsteroidal antiinflammatory drugs (NSAIDs) at 14%. Notably, 14% of the drug-related cases involved multiple drugs, and other drugs were implicated in 21% of cases. Further details on specific medications are provided in Supplementary Table S1.

Predictors for Kidney Recovery in the Entire Cohort

Across the entire cohort, univariable analysis identified White race, prebiopsy AIN diagnosis, a known cause of AIN, drug-related AIN, and CRP levels as factors associated with increased kidney recovery

Table 2. All causes of acute interstitial nephritis

Causes	Number of patients, n (%)
Drug-induced	111 (66.9) ^a
Antibiotics	40 (36.0)
PPIs	32 (28.8)
ICIs	20 (18.0)
NSAIDs	15 (13.5)
Other drugs	23 (20.7)
Multiple drugs	16 (14.4)
Autoimmune related	33 (19.9) ^a
Sjogren syndrome ^b	11 (33.3)
Sarcoidosis	7 (21.2)
TINU	3 (9.1)
VEXAS syndrome	3 (9.1)
IgG4-related	2 (6.1)
IBD	2 (6.1)
SLE	1 (3.0)
GPA	1 (3.0)
CVID	1 (3.0)
Crohn disease	1 (3.0)
RA and allergic rhinitis	1 (3.0)
Infectious	10 (6.0) ^a
Bacterial ^c	5 (50.0)
Viral ^d	1 (10.0)
Fungal ^e	4 (40.0)
Other	4 (2.4) ^a
Malignancy ^f	3 (75.0)
Calcium oxalate deposit	1 (25.0)
Multiple causes	7 (4.2)
Drug and autoimmune ^g	6 (85.7)
Drug and infectious disease ^h	1 (14.3)
Unknown	15 (9.0) ^a

CVID, common variable immunodeficiency; GPA, granulomatosis with polyangiitis; RA, rheumatoid arthritis; IBD, inflammatory bowel disease; ICIs, immune checkpoint inhibitors; NSAIDs, nonsteroidal antiinflammatory drugs; PPIs, proton pump inhibitors; SLE, systemic lupus erythematosus; TINU, tubulointerstitial nephritis and uveitis syndrome.

^aThe percentage in the entire cohort.

^bOne patient also had rheumatoid arthritis.

^cOne *Escherichia coli*, 1 *Klebsiella aerogenes*, 1 methicillin-sensitive *Staphylococcus aureus* (MSSA), 1 mycobacterium infection, and 1 *Streptococcus agalactiae*.

^dBK virus.

^eOne candida, 2 histoplasmosis, and 1 unidentified.

^fOne B cell chronic lymphocytic leukemia, 1 B cell lymphoma, and 1 multiple myeloma.

^gOne combination of antibiotic (sulfonamides) and Sjogren syndrome, 1 combination of antibiotic (penicillin and z-pak/azithromycin), PPI (omeprazole) and Sjogren syndrome, 1 combination of NSAID (ibuprofen) and Sjogren syndrome, 1 combination of PPI (esomeprazole) and IgG4-related disease, 1 combination of PPI (omeprazole) and SLE, and 1 combination of mesalamine and Crohn disease.

^hCombination of antibiotic (fluoroquinolones) and *E coli*.

(Table 3). Conversely, the presence of oliguria, IFTA, global glomerulosclerosis, and granulomas, as well as 24-hour proteinuria and the need for dialysis, were factors associated with decreased kidney recovery. Within the study cohort, 134 patients (81%) received steroid therapy. Univariable analysis indicated that steroid therapy was not significantly associated with kidney recovery ($P = 0.41$). Subsequent multivariable analysis indicated that only IFTA (OR: 0.15; 95% CI: 0.03–0.70; $P = 0.02$) and dialysis requirement (OR: 0.07; 95% CI: 0.01–0.64; $P = 0.02$) were significant predictors for decreased kidney recovery, whereas prebiopsy diagnosis of AIN was a strong indicator

Table 3. Univariable and multivariable analysis of predictors influencing kidney recovery in the entire cohort

Variables	Univariable analysis		Multivariable analysis	
	OR (95% CI) ^a	P value	OR (95% CI) ^{a,b}	P value
Age ^c	1 (0.99–1.02)	0.39	-	-
Male	0.98 (0.48–2.00)	0.97	-	-
White race	10.9 (3.0–62.2)	<0.0001	0.12 (0–136)	0.55
Prebiopsy AIN diagnosis	3.36 (1.53–7.42)	0.003	10.8 (1.7–69.3)	0.01
Drug-related	2.2 (1.1–4.6)	0.04	1.52 (0.31–7.52)	0.61
Known cause	3.2 (1.0–9.4)	0.04	1.13 (0.08–17.00)	0.93
Oliguria	0.38 (0.16–0.92)	0.033	1.69 (0.15–19.3)	0.78
IFTA (moderate/severe)	0.20 (0.09–0.42)	<0.0001	0.15 (0.03–0.70)	0.02
Global glomerulosclerosis (moderate/severe)	0.26 (0.11–0.58)	0.001	0.32 (0.07–1.52)	0.15
Granuloma present	0.4 (0.2–0.9)	0.04	0.71 (0.11–4.42)	0.71
24-h proteinuria	0.64 (0.46–0.85)	0.001	0.54 (0.21–1.35)	0.18
CRP ^c	1.01 (1.00–1.03)	0.046	1.01 (0.99–1.04)	0.16
Neutrophil count ^c	1.01 (0.94–1.21)	0.33	-	-
Dialysis required	0.11 (0.04–0.28)	<0.0001	0.07 (0.01–0.64)	0.02
Steroid treatment	1.4 (0.6–3.3)	0.41	-	-

AIN, acute interstitial nephritis; CI, confidence interval; CRP, C-reactive protein; IFTA, interstitial fibrosis and tubular atrophy.

^aOdds ratios (OR) with 95% CI and P values calculated using logistic regression model to identify factors associated with recovery in the entire cohort.

^bThe variables with $P < 0.05$ in univariable analysis were used for multivariable analysis.

^cOR is per unit change in regression.

(OR: 10.8; 95% CI: 1.7–69.3; $P = 0.01$) for increased kidney recovery.

We further assessed the effectiveness of steroid therapy on kidney outcomes by comparing these results with those of patients who did not receive steroid treatment (Supplementary Table S2). Most variables, including kidney outcomes within the first 6 months and the time to recovery, did not differ between the 2 groups; exceptions were lower peak sCr (3.6 mg/dl vs. 7 mg/dl, $P = 0.002$), need of dialysis (12% vs. 28%, $P = 0.03$), and incidence of ESKD (8% vs. 32%, $P = 0.004$), as well as higher albumin levels (3.8 ± 0.6 g/l vs. 3.2 ± 1.0 g/l, $P = 0.02$) observed in the steroid-treated group.

Effects of Steroid Therapy on Kidney Recovery in the Entire Cohort

Within the entire cohort, survival analysis demonstrated that steroid treatment did not influence kidney recovery (log-rank test: $P = 0.84$) (Figure 1). Further analysis, both unadjusted and adjusted for various variables revealed no significant difference in kidney recovery between patients who received steroid therapy and those who did not (Table 4).

Kidney Outcomes of Drug-Related AIN

Upon diagnosis of AIN, all drugs implicated in the condition were discontinued. According to the data in Supplementary Table S3, drug-induced AIN was

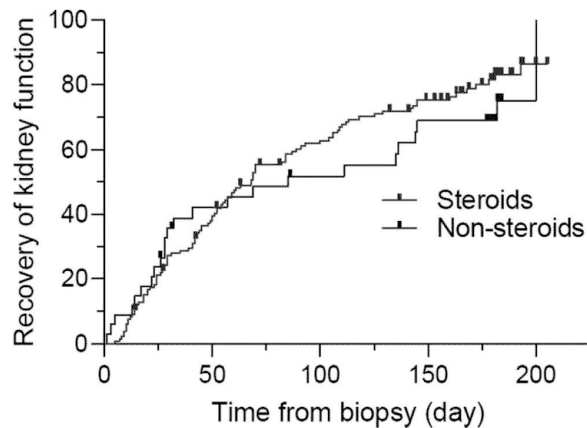


Figure 1. Kidney recovery between steroid and nonsteroid treatment in patients with AIN. One hundred thirty-three patients were treated with steroid, whereas 32 were not. The effectiveness of steroid therapy in achieving either complete or partial kidney recovery was evaluated through Kaplan-Meier analysis, with a log-rank test result of $P = 0.84$. The average recovery time for kidneys in patients receiving steroid treatment was 62 days, similar to the 64 days observed in patients who did not receive steroid treatment.

associated with a higher incidence of rash (17% vs. 4%, $P = 0.01$) and elevated CRP (23 mg/dl vs. 12 mg/dl, $P = 0.04$) and neutrophils ($5.6 \times 10^9/L$ vs. $4.3 \times 10^9/L$, $P = 0.01$). In addition, these patients had a lower prevalence of CKD prior to biopsy (30% vs. 51%, $P = 0.01$), as well as reduced granuloma formation (14% vs. 33%, $P = 0.01$). Although the proportion of drug-induced AIN with steroid therapy was comparable to those with other causes (85% vs. 73%, $P = 0.09$), the duration of steroid use was significantly shorter (median 8 weeks vs. 16 weeks, $P = 0.002$) in drug-induced AIN. Of the patients with drug-induced AIN, 81% achieved kidney recovery, significantly higher than the 66% observed in patients with other causes of AIN

Table 4. Comparative likelihood of kidney recovery in AIN: steroid vs. nonsteroid therapy

Variables	HR (95% CI) ^a	P value
Nonadjusted	1.32 (0.64–2.71)	0.46
Adjusted for		
Sex	1.41 (0.68–2.93)	0.36
White race	1.57 (0.71–3.52)	0.27
Prebiopsy AIN diagnosis	1.37 (0.66–2.89)	0.56
Oliguria	1.38 (0.66–2.88)	0.39
IFTA	1.29 (0.61–2.72)	0.50
Global glomerulosclerosis	1.44 (0.67–3.1)	0.36
Granuloma present	1.32 (0.64–2.72)	0.45
Known cause	1.25 (0.59–2.66)	0.56
Drug related	1.34 (0.64–2.78)	0.44
CRP	1.3 (0.41–4.19)	0.66
Dialysis required	1.39 (0.65–2.98)	0.39
All the above variables	3.86 (0.19–79.9)	0.38

AIN, acute interstitial nephritis; CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; IFTA, interstitial fibrosis and tubular atrophy.
^aHR and 95% CI calculated using proportional Cox hazard model.

($P = 0.04$). Approximately half of the patients with drug-induced AIN had normal kidney function at the 6-month follow-up, in contrast to the 79% of patients with other causes who developed ESKD or progressive CKD ($P = 0.004$).

We also conducted a comparison of the clinical characteristics between patients with drug-induced AIN who achieved recovery and those who did not recover (Supplementary Table S4). Compared to patients who experienced recovery, those without recovery exhibited a higher incidence of moderate to severe IFTA (57% vs. 19%, $P = 0.003$) and global glomerulosclerosis (43% vs. 15%, $P = 0.03$), along with a greater dialysis need (33% vs. 7%, $P = 0.003$). Conversely, their levels of CRP were lower (7.5 mg/dl vs. 32 mg/dl, $P = 0.03$). At the 6-month follow-up, kidney function normalized in 61% of the patients who achieved kidney recovery, whereas every patient who did not recover experienced either progressive CKD or progressed to ESKD.

The proportion of patients undergoing steroid therapy was consistent between the recovery and nonrecovery groups in cases of drug-related AIN (83% vs. 91%, $P = 0.52$), as shown in Supplementary Table S4. We evaluated kidney outcomes in patients with drug-induced AIN who received steroid therapy versus those who did not (Table 5). The proportion of kidney recovery was comparable between the 2 groups (80% vs. 88%, $P = 0.59$). Kidney outcomes at the 6-month follow-up were also similar ($P = 0.99$).

In this study, the distribution of patients with drug-induced AIN was as follows: 30 associated solely with antibiotics, 16 with PPIs, 18 with ICIs, and 7 with NSAIDs. Supplementary Table S5 details comparisons of clinicopathological features across these 4 categories. Most variables showed no significant differences between the groups. However, NSAID-related AIN exhibited a lower incidence of comorbidities compared to the other groups (57% vs. 97%–100%, $P = 0.001$). Nearly all patients in the ICI-related AIN group had normal or mild IFTA, whereas approximately one-third of patients in the other groups displayed moderate to severe IFTA ($P = 0.02$). Kidney interstitial eosinophils were also less prevalent in the ICI-related group compared to the other groups (33% vs. 50%–86%, $P = 0.002$). Only 43% of NSAID-related AIN received steroid therapy, compared to 80% in antibiotics and 94% in PPI or ICI groups ($P = 0.01$). The duration of steroid use was shortest in the antibiotics group (6 weeks vs. 8–10 weeks in other groups, $P = 0.02$). All patients with ICI-related AIN achieved recovery and none developed ESKD, whereas 29% of patients within NSAID group did not achieve recovery and 40% progressed to ESKD ($P = 0.03$).

Table 5. Kidney outcomes in drug and autoimmune-induced AIN: comparisons of steroid therapy and nonsteroid therapy

	Drug-induced AIN (<i>n</i> = 111)			Autoimmune-induced AIN (<i>n</i> = 27)	
	Steroid therapy (<i>n</i> = 94)	Nonsteroid therapy (<i>n</i> = 17)	<i>P</i> value	Steroid therapy (<i>n</i> = 27)	<i>P</i> value ^a
Mycophenolate mofetil, <i>n</i> (%)	3 (3.2)	0	>0.99	5 (18.5)	0.01
Recovery within 6 mo, <i>n</i>	94	17	0.59	27	0.06
Complete recovery, <i>n</i> (%)	49 (52.1)	11 (64.7)		14 (51.9)	
Partial recovery, <i>n</i> (%)	26 (27.7)	4 (23.5)		7 (25.9)	
No recovery, <i>n</i> (%)	19 (20.2)	2 (11.8)		6 (22.0)	
Time to recovery (d)	43 (21–84)	28 (17–135)	0.78	82 (44–166)	0.04
Time to start steroids (d)	1 (1–3)	na	na	6 (1–16)	0.03
Outcome at 6-month follow-up, <i>n</i>	69	12	0.99	26	0.06
Normal kidney function, <i>n</i> (%)	34 (49.3)	6 (50.0)		6 (23.1)	
Progressive CKD, <i>n</i> (%)	30 (43.5)	5 (41.7)		18 (69.2)	
ESKD, <i>n</i> (%)	5 (7.3)	1 (8.3)		2 (7.7)	

AIN, acute interstitial nephritis; CKD, chronic kidney disease; ESKD, end stage kidney disease; IQR, interquartile range; na, not applicable. Results are presented as median (IQR) for continuous variables and as *n* (%) for categorical variables.

^aThe *P* value for comparisons of patients with steroid therapy between drug- and autoimmune-related AIN.

In addition, all 27 patients with AIN solely affected by autoimmune disease were treated with steroids. Significantly, 5 patients with autoimmune-related AIN were treated with mycophenolate mofetil, in contrast to just 3 patients with drug-induced AIN who underwent steroid therapy ($P = 0.01$). Table 5 shows that for autoimmune-related AIN, steroids were initiated at a median of 6 days after biopsy. Of these cases, 78% ($n = 21$) experienced kidney recovery, with a median recovery period of 82 days. The time to initiate steroid therapy and the duration of kidney recovery for autoimmune-related AIN were considerably longer than for drug-induced AIN, where the median time were 1 day and 43 days, respectively, with statistically significant differences ($P = 0.03$ and $P = 0.04$). Notably, among patients who received steroid treatment, kidney recovery and outcomes were similar between drug-induced and autoimmune-related AIN ($P = 0.06$ for both).

Characteristics of Patients With AIN who Underwent Dialysis

Within the entire cohort, 25 patients required dialysis; of these, 36% (9 out of 25) achieved either complete or partial recovery. Meanwhile, 61% (11 out of 18) progressed to ESKD at the 6-month follow-up (Supplementary Table S6). Medications were the primary cause of AIN necessitating dialysis, representing more than half of the cases (52%, 13 out of 25). Importantly, 64% of patients who progressed to ESKD exhibited severe IFTA, whereas none of the patients without ESKD presented with severe IFTA ($P = 0.02$).

Predictors of Kidney Recovery in Drug-Induced AIN

Univariable analysis revealed that factors such as moderate to severe IFTA, global glomerulosclerosis, CKD prior to biopsy, and the necessity for dialysis were

associated with decreased kidney recovery; whereas steroid treatment was not a predictor of kidney recovery (Supplementary Table S7). Further multivariable analysis demonstrated that only moderate to severe IFTA (OR: 0.24; 95% CI: 0.06–0.85; $P = 0.03$) and the need for dialysis (OR: 0.17; 95% CI: 0.04–0.79; $P = 0.02$) remained significant predictors for decreased recovery.

Effects of Steroid Therapy on Kidney Recovery Within 6 Months in Drug-Induced AIN

Survival analysis, which included all 111 patients with drug-related AIN, showed that steroid treatment did not significantly affect kidney recovery within the initial 6 months (log-rank test: $P = 0.42$) (Figure 2). The results from both unadjusted and adjusted analyses (either sex, kidney size, IFTA, global glomerulosclerosis, CKD prior to biopsy, dialysis required, or all these variables) indicated that there was no significant difference in kidney recovery between patients who received steroids and those who did not (Table 6).

DISCUSSION

This study offers significant insights into the etiology, clinicopathological manifestations, and prognostic factors associated with AIN, as well as the impact of steroid therapy on kidney outcomes in the last decade. Our research demonstrates that the primary cause of AIN continues to be drug-induced, aligning with earlier studies that identify medications as the foremost contributors to AIN (Supplementary Table S8).^{1,8,12} Among these agents, antibiotics remain the most frequently implicated in AIN, although there is a decreasing trend compared to the previous period (24% versus 35%, $P = 0.07$). Notably, the incidence of AIN related to PPIs is increasing (19% vs. 10%, $P = 0.01$). Importantly, AIN associated with ICIs is emerging and

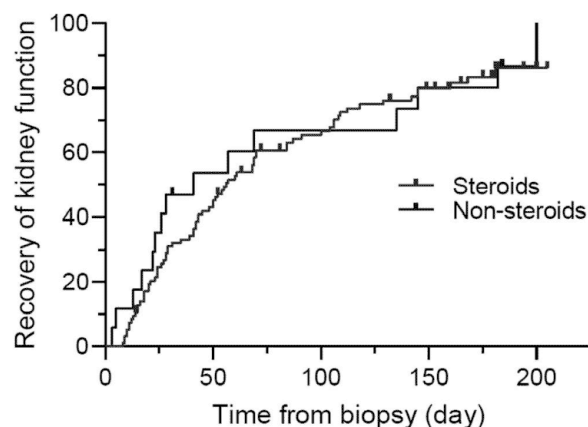


Figure 2. Kidney recovery between steroid and nonsteroid treatment in patients with drug-related AIN. Among 111 patients with drug-induced AIN, 94 received steroid therapy, whereas 17 did not. The effectiveness of steroid therapy in achieving either complete or partial kidney recovery was evaluated through Kaplan-Meier analysis, with a log-rank test result of $P = 0.42$. The average recovery time for kidneys in patients receiving steroid treatment was 56 days, similar to the 64 days observed in patients who did not receive steroid treatment.

now represents 12% of the entire cohort and 18% of drug-related AIN, paralleling the rising prevalence of cancer and the expanded use of ICIs.^{13–15} In our cohort, AIN related to ICIs has already surpassed that associated with NSAIDs. In addition, AIN related to ICI treatment frequently involves concurrent use of other drugs such as PPIs.¹⁶ In this study, 2 patients received both ICIs and additional drugs, accounting for 10% (2 out of 20) of ICI-related AIN. Specifically, one used a PPI, and the other was on antibiotics, a PPI, and an NSAID. Interestingly, the incidence of AIN with an unknown cause has increased from 1% during the 1993 to 2011 period to 9% currently ($P = 0.0001$), whereas the rate of prebiopsy diagnosis of AIN has also increased (78% compared to 55%, $P < 0.0001$). The percentage of patients receiving steroid therapy remained similar (86% during 1993–2011 vs. 81% in

the current period, $P = 0.21$). Whereas 6-month outcomes were comparable between the periods, the time to recovery appears to be shorter in the current period, with a median of 6.8 weeks compared to 12 weeks previously. These findings indicate a shift in etiology, characterized by increased use of PPIs and especially ICIs. Steroid therapy continues to be extensively utilized in patients with AIN. Whereas kidney outcomes were similar to those in earlier periods, recovery time has decreased in the current period, likely due to improved early recognition of this condition.

This retrospective analysis underscores the complexity and varied etiology of AIN, highlighting the significant variability in kidney outcomes among affected patients. The pivotal findings of this study elucidate the differential impact of underlying causes—predominantly drugs, autoimmune conditions, and infections—on kidney recovery. Significantly, drug-induced AIN was more amenable to recovery, contrasting with cases attributed to autoimmune diseases or infections, which were less likely to see kidney function restitution. The disparity in recovery rates might be attributable to the direct reversibility of drug effects upon cessation compared to the often-progressive nature of autoimmune or infectious etiologies.^{2,12} Remarkably, in cases of drug-induced AIN, patients recovered faster, typically within 1.7 months, compared to 3 months for other causes of AIN. Furthermore, a larger proportion of patients with drug-induced AIN reached recovery, whereas fewer progressed to ESKD relative to those with AIN from other causes. It is important to note that within the drug-induced AIN group, about 20% of patients who did not recover eventually died, and 40% advanced to ESKD.

As previously reported,¹⁷ the clinical presentation of AIN was varied, with only a minority of patients exhibiting the classic triad of rash, fever, and eosinophilia as well as relatively bland urine. This underscores the diagnostic challenge posed by AIN, necessitating a high index of suspicion and often reliance on kidney biopsy for definitive diagnosis.⁷ Laboratory findings such as elevated CRP and neutrophil counts were more pronounced in drug-related AIN, potentially reflecting a more robust inflammatory response in these cases.

Histopathologically, the presence of moderate to severe IFTA was significantly associated with worse kidney outcomes, consistent with previous studies.^{1,18,19} Nevertheless, a prebiopsy diagnosis of AIN was positively associated with kidney recovery. These findings underscore the critical need for early detection and intervention to prevent irreversible kidney damage. Although some studies have reported

Table 6. Comparative likelihood of kidney recovery in drug-related AIN: steroid versus nonsteroid therapy

Variables	HR (95% CI) ^a	P value
Nonadjusted	2.64 (0.61–11.45)	0.20
Adjusted for		
Sex	2.74 (0.63–11.92)	0.18
Kidney size	3.56 (0.48–26.2)	0.21
IFTA	2.72 (0.62–11.84)	0.18
Global glomerulosclerosis	2.67 (0.61–11.68)	0.19
CKD prior to biopsy	2.63 (0.60–11.56)	0.20
Dialysis required	2.61 (0.60–11.36)	0.20
All the above variables	3.24 (0.41–25.9)	0.27

CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; IFTA, interstitial fibrosis and tubular atrophy.

^aHR and 95% CI calculated using proportional Cox hazard model.

that greater interstitial inflammation correlates with better kidney function recovery,^{18,20} we were unable to assess this in our study due to the lack of a consistent quantification of the nonscarred cortex involved by inflammation. In addition, our data show that the need for dialysis at presentation strongly predicted poor recovery, reflecting the severity of kidney impairment in these patients. Notably, over half of those with severe IFTA progressed to ESKD by the 6-month follow-up. Other potential clinical or histological factors affecting AIN prognosis include advanced age, severity of tubulitis, and the presence of granulomas, though their impact remains uncertain.^{1,11,21,22}

Steroid therapy, frequently used for AIN, was promptly initiated in 80% of the cohort within 2 days after biopsy. The majority of patients with AIN related to antibiotics, PPIs, and ICI were treated with steroids. In contrast, only 43% of those with NSAID-related AIN received steroid therapy. Although steroids are traditionally believed to mitigate the inflammatory process in AIN, kidney outcomes over the initial 6 months were similar across these groups; analysis using proportional Cox regression and survival analysis indicated that steroid treatment had no impact on kidney recovery outcomes in both the overall AIN cohort and specifically within the drug-related AIN subgroup. This observation is especially pertinent in light of the current discussions surrounding the effectiveness of steroids in managing AIN.¹ Notably, several studies have demonstrated the benefits of employing steroids, especially when used early in cases of drug-induced AIN.^{5,23–25} It is important to recognize that the limited number of patients who did not receive steroids in the cohort, both for drug-related AIN and overall, complicates any comparative analysis and firm conclusion drawing; selection bias persists even after adjustments. Furthermore, the small size of the subgroup with non-drug-related AIN precluded analyses of prognostic factors and the effectiveness of steroids. Consequently, it is difficult to definitively conclude that steroids have no potential benefit in AIN. Further clinical trials are necessary to better determine the role of steroids in the treatment of AIN. The lack of significant benefit observed in this study may prompt a reevaluation of current treatment protocols and encourage exploration of alternative or adjunctive therapies.²¹

Although kidney outcomes did not differ between the steroid-treated group and the untreated group within the initial 6 months, by the end of this period, only 8% of the patients in the steroid-treated group developed ESKD, compared to 29% in the nonsteroid group. This indicates that steroids may have a prolonged protective effect against the progression of

AIN.⁹ A recent randomized clinical trial suggested that prednisolone may improve long-term outcomes of CKD in patients with an unknown etiology.²⁶ Notably, all patients with ICI-related AIN experienced some level of kidney recovery, either complete or partial. This group also displayed minimal or absent IFTA and had the lowest presence of eosinophils compared to those with AIN related to antibiotics, PPIs, and NSAIDs. By the end of the 6-month follow-up, 40% of the NSAID-related AIN group had progressed to ESKD, whereas none in the ICI and PPI groups did, and only a small portion of the antibiotic-related group developed ESKD. In cases of drug-related AIN, the presence of IFTA and the necessity for dialysis were also identified as risk factors impacting kidney recovery. This observation calls into question the conventional reliance on corticosteroids for managing AIN, particularly when considering the risks associated with long-term steroid use, such as infections and metabolic disturbances. This aspect of treatment demands a reevaluation, potentially paving the way for clinical trials to establish more refined criteria for steroid administration in patients with AIN.

We acknowledge several limitations of this study. First, the retrospective design inherently limits our ability to ascertain causal relationships and may be subject to biases related to data collection and selection. Second, the identification of AIN was exclusively dependent on biopsy, potentially excluding patients with clinical AIN who did not undergo this procedure, thereby introducing selection bias. The variability in treatment approaches, because not all patients received standardized therapy, could influence the outcomes independently of the disease process itself. Furthermore, the study may not have adequately controlled for all potential confounding variables that could influence the outcomes, such as variations in the severity of initial kidney injury, patient comorbidities, or the precise timing and dosage of steroid therapy.

In conclusion, the study offers crucial insights into the determinants of kidney recovery in AIN, demonstrating that though the cessation of causative agents and management strategies, including steroid therapy, are standard, their effectiveness varies substantially across different patient subgroups. The potential benefits of steroid therapy in patients with AIN cannot be ruled out, underscoring the necessity of additional clinical trials. Crucially, the extent and severity of irreversible kidney damage present at the time of biopsy significantly influences outcomes. Although this assumption is widely held, data from large cohorts underscore the importance of early intervention and setting realistic expectations for recovery. Future research should focus on refining treatment protocols,

exploring novel therapies, and conducting long-term follow-up studies to enhance kidney recovery in patients with AIN. These findings contribute to a deeper understanding of AIN and provide a foundation for improving patient care and outcomes in this challenging clinical condition.

DISCLOSURE

All the authors declared no competing interests.

DATA AVAILABILITY STATEMENT

Data are available upon reasonable request to the corresponding author.

AUTHOR CONTRIBUTIONS

JM and WC conceptualized and designed the study. JM and PK acquired the data. JM and CT performed data analysis. JM wrote the initial draft, with WC performing primary revisions. AB and IMC contributed to the discussion of the results. All the authors revised the manuscript and approved the final version of the article.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Causes of drug-related AIN.

Table S2. Clinical, laboratory, histopathological, and outcome comparisons in the entire AIN cohort: steroid therapy vs. nonsteroid therapy.

Table S3. Clinical, laboratory, histopathological, treatment and outcome comparisons between drug-related and all other causes related AIN.

Table S4. Clinical, laboratory, histopathological, and treatment comparisons in the drug-related AIN cohort: recovery vs. nonrecovery.

Table S5. Clinical, laboratory, histopathological, treatment and outcome comparisons among different drug-related AIN.

Table S6. Characteristics of patients with AIN on dialysis.

Table S7. Univariable and multivariable analysis of predictors influencing kidney recovery in the drug-related AIN.

Table S8. Comparison of the etiology spectrum, clinicopathological features, and kidney outcomes between the current period (2012–2023) and the previous period (1993–2011).

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Facing the Challenge of Drug-Induced Acute Interstitial Nephritis

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Keywords

Interstitial nephritis · Acute kidney injury · Drug-induced acute interstitial nephritis treatment · Pathogenesis · Prognosis glucocorticoids

Abstract

Background: Acute interstitial nephritis (AIN) is one of the chief causes of acute kidney injury (AKI). AIN might be produced by drugs, infections, autoimmune diseases, or can be idiopathic. Among these etiologies, drug-induced AIN (DI-AIN) is the dominant one in many countries. Even when DI-AIN is suspected, identification of the putative drug is challenging. **Summary:** DI-AIN is an increasingly common cause of AKI. Diagnosis continues to pose a challenge for physicians due to nonspecific clinical symptoms, and the fact that it can be triggered by a wide variety of medications. Furthermore, the gold standard for the diagnosis is kidney biopsy. All these aspects render the diagnosis more difficult. The withdrawal of the causative drug of DI-AIN is the centerpiece of the treatment, and if early restoration of original kidney function is not obtained, several studies support the treatment with steroids especially when they are started quickly. **Key Messages:** Almost all drugs have the potential to produce drug-induced acute interstitial nephritis (DI-AIN); however, antibiotics, nonsteroidal anti-inflammatory agents,

and proton pump inhibitors account for the majority of the reported cases. DI-AIN is produced by an idiosyncratic delayed type IV hypersensitivity reaction, but the precise pathophysiological mechanism remains to be elucidated. DI-AIN symptoms are nonspecific, and most of the patients will present mild symptoms including malaise, nausea, and vomiting. The classical triad, associating fever, rash, and eosinophilia, is seldom present. Nonoliguric acute kidney injury is the main renal manifestation of DI-AIN. Tubular non-nephrotic range proteinuria is usually present. Diagnosis of DI-AIN relies on maintaining a high index of suspicion in those patients at greater risk, but kidney biopsy is required to confirm diagnosis. Histologically, AIN is characterized by the presence of an extensive interstitial infiltrate, mainly composed of lymphocytes and monocytes, but eosinophils, plasma cells, histiocytes, and polymorphonuclear cells can also be found. The withdrawal of the presumed causative drug of DI-AIN is the mainstay of the treatment. When there is no evidence of kidney function recovery after an interval of 5–7 days since interrupting the treatment with the suspected drug, several studies support the treatment with steroids, especially when they are promptly started. Early corticosteroids would decrease the inflammatory infiltrates of the kidney interstitium, thus preventing the risk of subsequent fibrosis.

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Introduction

Acute interstitial nephritis (AIN) is one of the leading causes of acute kidney injury (AKI), and probably, the real frequency is underestimated since a significant number of AKI of unclear etiology would correspond to AIN if a noninvasive diagnostic tool rather than a kidney biopsy was available. Histologically, it is characterized by inflammatory infiltrates in the kidney interstitium, with usually preserved glomerulus and vessels. This disease was first described in 1898, mainly associated with infectious diseases [1]. However, this changed during the XX century when drug-induced AIN (DI-AIN) started to be relevant, currently assuming 85% of AIN cases. The first cases of DI-AIN were 7 patients with penicillin-induced AIN. Since then, a considerable number of cases and multiple drugs have been involved.

Currently, DI-AIN roughly represents the leading cause of AIN in many countries, but infectious AIN is still an important cause of AIN in less developed countries. It has been estimated that DI-AIN is the third most common cause of AKI in hospitalized patients [2].

It is difficult to assess the exact prevalence of DI-AIN since studies are based on retrospective analysis and most notably because the gold standard for the diagnosis is kidney biopsy. According to biopsy data registries, it is possible to extrapolate an approximate prevalence of the disease. Globally, it has been estimated that on average between 0.5% and 5% of all kidney biopsies performed have the disease [3]. Nevertheless, this percentage increases up to 27% if the biopsy is performed in the setting of an AKI [2]. In the Spanish Registry of Glomerulonephritis, the percentage of biopsies meeting this diagnosis has increased from 3.6% to 10.5% during the past decade, with a more pronounced increase in the elderly population (from 1.6% to 12.3%). Such an increase is apparently linked to the generalized use of antibiotics and other over-the-counter medications such as proton pump inhibitors (PPIs) and nonsteroidal anti-inflammatory agents (NSAIDs) in most countries. DI-AIN is highly prevalent among the elderly with an estimated prevalence of 19% [4]. These differences could be explained by several points: chronic medication and over-the-counter medication are more common among older patients, they tend to present some degree of renal impairment, and to the fact that kidney biopsies are nowadays performed more frequently in this group.

To date, three major drug classes (antibiotics, NSAIDs, and PPIs) accounted for 80–90% of the reported cases of DI-AIN. However, a new class of medications, immune

checkpoint inhibitors (ICIs), has increasingly gained attention as a cause of AIN [5]. These new drugs pose the same diagnostic or therapeutic challenges as other DI-AIN, but they add an important ethical question since in some patients there is not an alternative treatment, and therefore, the treatment with ICIs cannot be discontinued.

Pathogenesis

It has been suggested that the underlying mechanism of DI-AIN would be a type IV idiosyncratic delayed hypersensitivity reaction mediated by T cells. This hypothesis is supported by several observations: eosinophils are commonly found in kidney biopsy, T cells are found to be the dominant lymphocytes forming sometimes granulomas, the symptoms of AIN remind those of a systemic hypersensitivity reaction, the time course of disease, and the negative immunofluorescence (IF) staining for immunoglobulins, and complement favor all together a type IV hypersensitivity reaction theory [6, 7].

Several mechanisms have been proposed to explain how drugs can exert hypersensitivity responses, but the precise physiopathological mechanism is still unknown (Fig. 1). It is possible that more than one pathological mechanism contributes to the final renal damage, which depends on the putative drug [6, 8].

One of the most widespread theories to explain the pathogenesis of the disease is the formation of haptens. Some drugs might have the ability to become immunogenic by binding to proteins through covalent links [8–11]. This new complex, termed hapten, has the capacity to act as an immunogenic antigen, and thus, it would be able to stimulate an immune response. This process can occur locally in the kidney, where drugs will bind to renal-specific tubulointerstitial proteins or in the peripheral circulation, that is, beta-lactam antibiotics. If haptenization occurs peripherally, the haptens will be carried out to the kidneys, where they will become “trapped”, and subsequently, filtered and endocytosed by the tubular epithelial cells of the kidney, starting the first phase of the immunogenic process, the antigen-recognition and presentation phase [10].

Tubular epithelial cells will process and metabolize the antigens, and then they will be presented to dendritic cells (DCs). DCs are located in the kidney interstitium, but they are in tight contact with tubular epithelial cells through their long-foot processes. This allows them to detect any problem and to further propagate cell injury

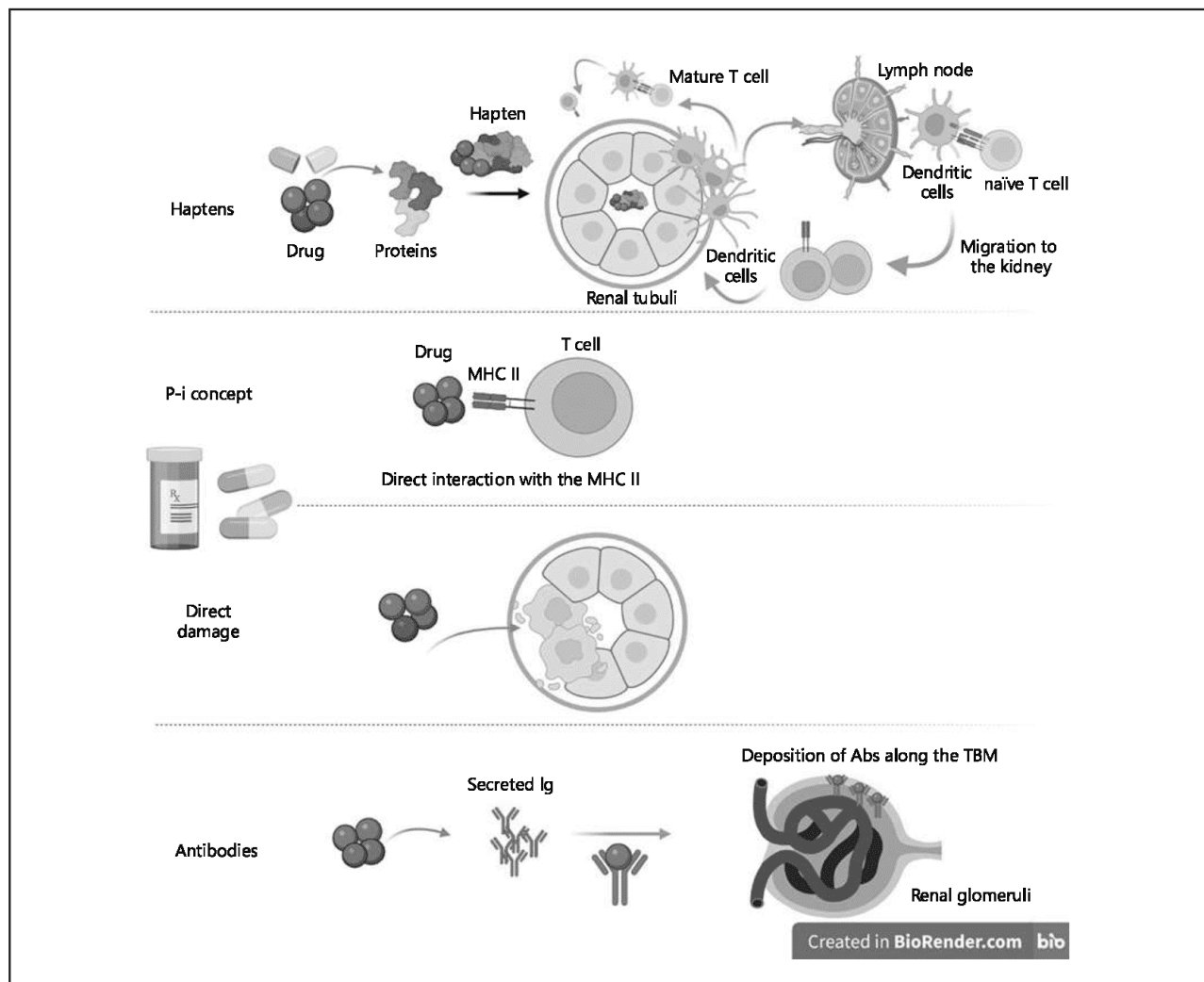


Fig. 1. DI-AIN pathogenesis. The pathogenesis of DI-AIN is driven by different mechanisms. Haptens: drugs might have the ability to form protein complex termed “haptens” which elicit renal damage after recognition by DCs and subsequent T-cell-mediated toxicity. P-i concept: Some drugs with some special structural features might stimulate T cells allowing a noncovalent bind to the major

histocompatibility peptide complex. This method has some similarities to superantigen stimulations. Direct damage: drugs might cause direct tubular damage. Antibodies: even if cytotoxic T-cell injury is most frequently involved in pathogenesis of AIN, there are some cases related to antibody-mediated damage.

[12]. When DCs are exposed to antigens, they become active by expressing the antigenic compounds as peptides on their surface major histocompatibility complex II molecules. Thereafter, DCs migrate from the kidneys to the regional lymph nodes to present the antigen to naïve T cells, which are then activated, and migrate to the antigenic source of injury.

Damaged cells will become activated, and they will generate proinflammatory chemokines and cytokines that

will induce the recruitment of macrophages and the proliferation of fibroblasts [13]. Due to the massive proliferation of fibroblasts, there will be an increased amount of extracellular matrix by epithelial-mesenchymal transition process. This reaction is associated with tubular cell damage and kidney damage, which in the long term could lead to fibrosis and chronic kidney disease (CKD) [10, 14, 15].

DI-AIN is mainly a cell-mediated process. This hypothesis is supported by the observation that T cells are

the predominant lymphocytes in DI-AIN renal biopsies [8]. Another fundament is the observation of drug-specific T cells in the peripheral blood of patients with biopsy-proven DI-AIN with simultaneous demonstration by immunohistochemistry of these T lymphocytes (either CD4+ or CD8+) in the kidney interstitium on kidney biopsy specimens [9, 16].

Alternatively, it has been described that drugs might directly interact with the immune receptors such as the T-cell receptor or the major histocompatibility complex. This process has been designated as “pharmacological interaction with immune receptors” or the p-i concept. This “pharmacologic” interaction can lead to T-cell activation and expansion, thereby producing an immunogenic response [11, 17].

However, it seems that there might be other relevant pathophysiological mechanisms that contribute to triggering this process. Therefore, several hypotheses have been proposed to explain the pathogenesis of the disease.

It has been hypothesized that drugs might produce a direct toxic damage to interstitial kidney structures that would render them immunogenic. Injured cells will secrete proinflammatory chemokines and cytokines that will attract inflammatory cells and induce the proliferation of fibroblasts that ultimately cause interstitial fibrosis [6, 18]. A second theory proposes that drugs could elicit an immune response by mimicking self-peptides due to structural similarities, thereby producing a cross-reactivity reaction between the tubular basement membrane (TBM) and the interstitial antigen [6, 19].

Some human leukocyte antigen (HLA) genotypes have been found to be associated with AIN. Cheng et al. [20, 21] demonstrated that HLA-DR was expressed in the majority of the patients with DI-AIN included in their study. Moreover, HLA-DR expression correlated to the severity of tubular atrophy and interstitial fibrosis. In addition, there was a positive correlation between the number of DR-positive cells in the interstitium and tubules [20, 21]. Accordingly, other studies have studied the susceptibility to the disease among other HLA genotypes. HLA-DQ seems to be implicated in pathogenesis. According to a single-center prospective cohort, HLA-DQA1, -DQB1, and -DRB1 are risk alleles both for DI-AIN and TINU syndrome. Histologically, this study showed that there were positive correlations between the number of interstitial CD4+ T lymphocytes and the tubular expression of HLA-DR and HLA-DQ. In the same way, the infiltration of monocytes/macrophages into the interstitial compartment and into the renal tubular wall was closely correlated with the tubular expression of HLA-DR and HLA-DQ [22].

Even if the injury in DI-AIN is mainly cell-mediated, the immune reaction in AIN can also be driven by the antibody-mediated immunity in a minor proportion of cases. It has been described in some cases that antigen-antibody complexes can deposit in the kidney, leading to kidney injury [14]. Even so, this is a rare finding, and it is often associated with tubulointerstitial injury. In these patients, IF staining demonstrates linear IgG deposition along the TBM. For example, methicillin is known to induce DI-AIN by the deposition of a granular immune complex along the TBM [23]. Some reports of methicillin-induced AIN have identified antibodies targeting a specific hapten in the TBM. Other drugs such as NSAIDs, phenylhydantoin, and allopurinol might also cause positive IF staining. Rifampicin-induced AIN is associated with the production of anti-rifampicin antibodies. It is likely that in DI-AIN, the same pathological pattern is the product of different triggers, and it is induced by distinct mechanisms as it happens in other kidney disorders.

The duration and severity of the effector phase will depend on the duration of the renal insult. In case of an intense and long exposition to the antigen, tubular epithelial cells will produce inflammatory chemokines and cytokines (TGF- β , IL1, IL4, lipid peroxidation products, ET-1, IGF-1, PDGF-BB) that will elicit activation of endothelial cells, the recruitment of fibroblasts, and the irreversible process of tubulointerstitial fibrosis [15].

Etiology

The most common causes of AIN can be clustered in drug-induced, infections-related, autoimmune diseases and idiopathic forms, being the first one responsible for more than two-thirds of the cases, followed by infection-related AIN in 15% of cases. Etiology of AIN changes with aging since the elderly tend to have more frequent DI-AIN, especially due to PPIs and penicillin, and a lower incidence of AIN due to autoimmune diseases or systemic causes [4].

A large number of drugs can be implicated in the pathogenesis of the disease, and at least from a theoretical point of view, any drug can induce AIN (Table 1). However, NSAIDs, PPIs, and antibiotics continue to be the most common drugs involved in AIN [24].

In the study conducted by Murithi et al. [25], antibiotics were the most prevalent cause (49%), followed by PPIs (14%) and NSAIDs (11%). Valluri et al. [26] reported that antibiotics and PPIs were the most prevalent causes of

Table 1. DI-AIN etiologies

Drug class	Examples	Time	Symptoms	Characteristics
Antibiotics	Beta-lactams: methicillin	Early onset of AKI (after some days or weeks)	Features of an allergic reaction (skin rash, fever, and eosinophilia) Fever is the most common feature Rash and/or arthralgias are less common Macroscopic hematuria Pyuria (with or without leukocyte casts)	2–3:1 male-to-female ratio Older children and young adults Extra-renal manifestations usually disappear after 2 weeks Time to complete renal recovery awaits 1.5 months Anti-TBM antibodies
	Non-beta-lactams: rifampicin		Headache Chills, dark-colored urine without hematuria Oliguric acute renal failure Hemolytic anemia: thrombocytopenia and hemolysis Hepatitis Renal glycosuria	Equal rate between males and females Dose-dependent mechanism associated with the production of anti-rifampicin antibodies The majority of these patients require acute dialysis, but most although not all, subsequently recover renal function Two-thirds of patients require renal transplantation
	Vancomycin		Inconsistent pyuria	Noninfectious granulomas might be observed
NSAIDs	Nonselective COX inhibitors: fenoprofen, ibuprofen, naproxen COX-2 inhibitors: celecoxib and rofecoxib	Long duration of treatment prior to development of AIN (6–18 months)	Systemic allergic symptoms (fever, rash, or eosinophilia) are rare Nephrotic syndrome Older populations have a higher risk Nephrotic range proteinuria is more common Hematuria is rare	Less intense interstitial inflammation and tubulitis and eosinophils are not predominant; sometimes granulomas, papillary necrosis, MCD, and membranous nephropathy
Antiviral	Abacavir Indinavir Aciclovir Atazanavir		Eosinophiluria Crystalluria	
PPIs	Omeprazole, lansoprazole, pantoprazole, esomeprazole	1 week to 9 months. Commonest 10–11 weeks	Rarely present with triad Hypersensitivity symptoms Inconsistent pyuria	Less severe AKI but lower probability of recovery by 6 months
5-Amino-salicylates	Sulfasalazine, mesalamine, olsalazine	During the initial year of therapy	Fever and rash in <10% of patients Inconsistent pyuria Idiosyncrasy	
Allopurinol			Exfoliative rash (sometimes severe) Inconsistent pyuria	
Antineoplastic agents	ICIs (ipilimumab, nivolumab, pembrolizumab) Lenalidomide	1–24 months ICIs: large latency period from drug administration	Extrarenal manifestations such as hypophysitis or colitis may precede AKI ICIs: milder creatinine elevation, leukocyturia	ICIs: Slow decrease in creatinine after treatment

DI-AIN can be produced by several medications. This table comprises the most frequent responsible agents. AKI, acute kidney injury; ICIs, immune checkpoint inhibitors; NSAIDs, nonsteroidal anti-inflammatory agents; PPIs, proton pump inhibitors.

DI-AIN in their cohort (35%) followed by NSAIDs (20%). The multicenter retrospective study by González et al. [27] showed that antibiotics and NSAIDs were the two primary offending classes of drugs, comprising 93% of the patients. It is possible that the pattern is changing, and recently, Fernández-Juárez et al. [28] reported that the most frequently offending drugs were NSAIDs (27%), followed by antibiotics (22%) and PPIs (4%).

With regard to antimicrobial agents, beta-lactam antibiotics are the most frequently involved drugs, and methicillin is the most well-documented drug. Methicillin is reported to induce AIN in up to 17% of the patients who have received at least 10 days of treatment [29]. It is characteristic that kidney injury appears days after drug intake. Extrarenal manifestations are characterized by hypersensitivity reaction features (skin rash, fever, and

eosinophilia), with fever being the most common manifestation, whereas rash and/or arthralgia are less common.

Although NSAIDs can induce kidney injury by several mechanisms, these drugs are well-known causes of DI-AIN and have become one of the most frequent causes. Most individuals are older than 50 years and are chronic users. Elderly patients are at a particularly high risk as they commonly take NSAIDs and have underlying comorbidities that increase their overall risk. Although all NSAIDs can be pathogenic, some nonselective NSAIDs are less toxic than others as they produce fewer effects on kidney prostaglandins, that is, low-dose aspirin, low-dose ibuprofen, and sulindac [14, 30, 31]. Clinically, NSAID-induced AIN is characterized by fewer extrarenal symptoms and longer latency periods.

Current use of PPIs is associated with a significantly increased risk of AIN. According to a nested case-control study, the crude incidence rate of PPI-related DI-AIN is estimated in 11.98 (95% CI 9.11–15.47) per 100,000 person-years [32]. PPIs are one of the more widely prescribed medications worldwide. These drugs are often perceived as safe, but the use of PPIs beyond their established indications is dangerous because it can produce a substantial kidney impact. According to some reports, PPIs are the second most frequent cause of DI-AIN, accounting for 14–64% of the cases [33, 34]. Its clinical presentation is nonspecific, and the interval within the drug use and the onset of AIN ranges between 1 week and 9 months. The severity of AKI in PPI-induced AIN may be lower compared to other drugs like antibiotics, but the probability of recovery is also lower [25].

This could be explained by the longer duration of treatment and the consequent greater exposure to the drug. These characteristics draw a kidney injury that is especially challenging in its diagnosis and whose clinical expression would be more compatible with CKD than with AKI episodes. In fact, recent studies have focused on analyzing the effect of PPIs on long-term kidney function, and the results suggested that omeprazole might be associated with an increased risk of CKD [33, 34].

In a large northern European cohort analysis comparing new users of PPIs and histamine H₂-receptor antagonists, PPIs users were at increased risk of suffering worse kidney outcomes. Indeed, they were at higher risk of doubling creatinine levels (hazard ratio [HR]: 1.26, 95% CI 1.05–1.51), of decreasing eGFR more than 30% (HR: 1.26; 95% CI 1.16–1.36), and for the development of end-stage kidney disease (HR: 2.4; 95% CI: 0.76–7.58) and AKI (HR: 1.3; 95% CI: 1–1.69). However, the results should be treat-

ed with caution as the results have weaknesses that limit conclusions about causality because the strength of the association was modest (HR: 1.26 for both), and there is considerable potential for residual confusion [35, 36].

In the last decade, drugs such as 5-aminosalicylic acid or new therapies against cancer like ICIs have started to play an important role in the pathogenesis of this disease. ICIs, such as nivolumab, ipilimumab, or pembrolizumab, have recently been described as causes of AIN with similar clinical and histologic features to the rest of DI-AIN but with longer latency periods. However, the etiopathogenesis can be due to a change in the immune system that can cause a loss of tolerance against endogenous antigens or that ICI reduces tolerance to other coexisting drugs implicated in AIN. Some articles have shown a close relationship with concomitant use of PPIs [37].

Cortazar et al. [38–40], reported that concomitant use of PPIs was a risk factor for DI-AIN together with dual ICI therapy and baseline eGFR <30 mL/min/1.73 m². Accordingly, combination treatment with more than one ICI increases the probability to develop DI-AIN, and also the severity of the eventual episode [41–43].

Clinical Manifestations

Symptoms are highly variable, and most of the patients will present mild symptoms. Therefore, diagnosis of DI-AIN relies on maintaining a high index of suspicion in those patients at higher risk for this disease, but, in the end, kidney biopsy is still needed to confirm AIN diagnosis.

In the majority of cases, AIN-related symptoms are nonspecific, including malaise, nausea, and vomiting. However, many patients are asymptomatic. The classical triad, composed of fever, rash, and eosinophilia, is seldom present accounting for 10% of the cases [44]. However, when this entity was initially reported, this triad was more frequently found. Some agents, such as NSAIDs and PPIs, are less commonly associated with fever, rash, or eosinophilia compared with other agents.

Skin eruptions are usually maculopapular or morbiliform, although diffuse erythroderma versus toxic epidermal necrolysis may also develop [2, 45]. On the other hand, fever can be low grade or intermittent but it can be absent [45].

Regarding the interval of time between the start of the drug and the episode of DI-AIN, beta-lactams and cephalosporins usually have a close correlation between drug initiation and the development of AIN. However, PPIs

and NSAID-induced kidney injury occur with longer drug exposure [4, 34]. When we analyzed ICI-related DI-AIN, there is a longer latency period from drug administration to diagnosis of DI-AIN compared to other drugs and a slower decrease in creatinine after treatment [3]. Rifampin is unique in that the interstitial nephritis generally occurs when the antibiotic is reintroduced after an interval, and the latent period may be as short as 1 day.

Renal Manifestations

Nonoliguric AKI is present in every DI-AIN case. Hyperkalemic, hyperchloremic metabolic acidosis, inconsistent with the degree of kidney failure, may be present and provides a clue that the tubulointerstitium is the site of kidney injury [46].

Tubular nonnephrotic range proteinuria is usually present in the setting of DI-AIN (90% of the patients). Proteinuria range usually varies from 0.7 to 1.5 g/24 h. Older individuals might be more likely to have a higher degree of proteinuria [47]. The incidence of nephrotic syndrome seems to be low and accounts for around 2.5–3% of the patients [2, 28, 48]. Patients with NSAIDs related to AIN tend to present higher proteinuria levels than other types of drugs inducing AIN, and nephrotic-range proteinuria seems to be a specific complication of NSAIDs. Nephrotic syndrome has been only exceptionally reported with other types of drugs such as methicillin [49]. In this setting, nephrotic proteinuria has been reported in 80% of the patients, more often associated with fenoprofen, naproxen, and ibuprofen or selective COX-2 inhibitors [50]. Nevertheless, in some patients, nephrotic proteinuria might be due to an underlying disease, so its presence might raise the suspicion for a concomitant diabetic kidney disease or another underlying glomerular disease [51]. In these cases, it is highly recommended evaluating previous blood and urine tests.

Despite the foregoing, the absence of nephrotic range proteinuria does not exclude the possibility of NSAID-related AIN because in some published series, a much lower prevalence has been documented. To explain the susceptibility to proteinuria caused by NSAIDs, it has been hypothesized that the underlying pathogenic mechanism would be a decrease in the synthesis of prostaglandins induced by NSAIDs, which could lead in an increased conversion of arachidonic acid to leukotrienes, producing an activation of T-helper cells inducing diffuse podocytes damage [52]. Extrarenal manifestations (low-grade fever, skin rash, and eosinophilia) that are frequent-

ly observed in AIN associated with antibiotics and other drugs are characteristically absent in NSAID-induced AIN [52, 53]. Urinalysis will present diverse abnormalities such as sterile pyuria in up to two-thirds of the cases; leukocyte casts (3–14%), and hematuria [40, 54].

In early clinical case reports, in which methicillin was the predominant putative agent, macroscopic hematuria appeared as a common finding of this entity; however, it is currently a very rare initial presentation [55]. While microscopic hematuria is more common, and it is found in nearly two-thirds of the patients, the presence of hematuria is known to be associated with a more severe disease and worse kidney outcomes [56]. The presence of red-blood-cell casts was once thought to be specific for glomerular disease; however, up to one-third of AIN patients exhibit red-blood-cell casts, probably related to disruption of interstitial blood vessels and leakage of erythrocytes to the tubular lumen [57]. Acute tubulointerstitial injury can induce tubular dysfunction, clinically detected as glycosuria. In a study of our group, glycosuria was present in the 21% of biopsy-proven AIN cases, compared to the 4% in those AKI due to other etiologies. The specificity for glycosuria and AIN was 99% (95% CI: 97–99%). Further studies are needed to confirm this finding [58].

Eosinophiluria

The presence of urinary eosinophils may be explained by the release of eosinophil granules after activation, with the potential for leaking into the tubules and being excreted into the urine [59]. Even if eosinophiluria was traditionally considered a classical biomarker in AIN, the presence of eosinophiluria in the urinary sediment is a nonspecific, and unreliable finding since it can be seen in many other kidney diseases such as renal abnormalities, urinary tract infections, acute tubular necrosis, and glomerulonephritis. Muriithi et al. [60] identified 566 patients with CKD caused by different etiologies, including 91 patients with AIN, 80% of them with DI-AIN. They found eosinophiluria in a variety of diagnoses besides AIN. Using a >1% urinary eosinophils cut-off, only 31% of AIN patients were identified, with a similar rate in acute tubular necrosis (29%). When increasing the cut-off up to 5%, sensitivity declined, but specificity improved. However, eosinophiluria was a poor test to discriminate against AIN and other kidney diseases [60]. In another study conducted in 1994 comprising 51 patients with suspected AIN, the sensitivity of eosinophiluria was 40% for the detection of AIN, and the positive predictive value

was 38% [24]. Hansel stain has been considered as a better method to visualize urinary eosinophils than Wright's stain [59].

Sterile Pyuria

Sterile pyuria is a common nonspecific finding (50–75% of the patients), especially in the setting of antibiotics related to AIN.

Urinary Sodium

It is a common belief that urine sodium concentration and fractional excretion of sodium would be low in these patients, but the reality is that it is unhelpful in the diagnosis of AIN as both can be either elevated or depressed [51].

Histology

The definitive diagnosis of AIN is given by the kidney biopsy. However, as previously mentioned, kidney biopsy is not always performed because on many occasions, we are faced with fragile patients, mild increase of serum creatinine, or at high risk of complications of the technique, assuming the diagnosis of this entity.

Histologically, it is characterized by the presence of an extensive interstitial infiltrate, mainly composed of lymphocytes and monocytes, but eosinophils, plasma cells, histiocytes, and polymorphonuclear cells can also be found. When immunohistochemical techniques are performed, the mononuclear component in drug-associated cases is mostly T lymphocytes.

It can also associate images of tubulitis and, accompanying this, typically, there are tubular degeneration signs such as loss of brush border, flattening of the epithelium, and desquamation of cells toward the tubular lumen. Regenerative changes such as mitosis and enlarged nuclei with prominent nucleoli can be found.

Initially, the inflammatory infiltrate can be associated with interstitial edema, but with time, it can develop fibrosis and tubular atrophy, these findings being characteristic of chronic interstitial nephritis. Elderly patients tend to present with a higher percentage of sclerotic glomeruli and more interstitial fibrosis and tubular atrophy [4]. Both the glomerular and vascular compartments are usually normal except when they have some other associ-

ated pathology, something that is always important to rule out.

IF does not usually show immune deposits, and fibrinogen deposits can be detected in the interstitium. In those associated with penicillins and cephalosporins, sporadic cases have been described with the presence of linear IgG and C3 in tubular bases. At the electron microscope level, no specific findings are detected.

Granulomatous interstitial nephritis is a different, but less common, form of presentation. It is associated with drugs such as NSAIDs, antimicrobials like vancomycin or ciprofloxacin, and also granulomatous diseases like sarcoidosis or TINU syndrome. Granulomas are mainly composed of macrophages and multinucleated giant cells.

Treatment

There is general agreement that withdrawal of the presumed causative drug is the mainstay of the treatment of DI-AIN. But even when DI-AIN is suspected, identification of the putative drug is challenging for several reasons among others due to the large list of possible putative drugs implicated in DI-AIN, the time from starting the drug to AKI is quite ranged, and the lack of precise screening methods to discriminate the offending drug [3].

This situation is even more complicated with the ever more widespread use of over-the-counter medicines such as NSAIDs or PPIs. Patients usually perceive these drugs as secure with low side-effect profile, and patients usually take them for chronic conditions during months or even years increasing the risk for side adverse effects [34, 61–63]. In these situations, only an in-depth focused interview can uncover the uptake of this kind of drugs. Another difficult situation are those patients treated with polypharmacy, especially those with chronic diseases and the elderly, which are at a particularly high risk for DI-AIN for their inherent fragility, eventual impaired kidney function and other comorbidities [64].

Despite all the efforts to identify the responsible drug, sometimes the culprit drug cannot be withdrawn or substituted due to its inherent benefits. This situation occurs frequently in AIN induced by chemotherapeutic drugs, specifically by ICI.

When there is no evidence of kidney function recovery after a 5–7-day period since interrupting the treatment with the suspected drug, many studies support the treatment with steroids, especially when they are promptly started (Fig. 2). The rationale for this approach is that ear-

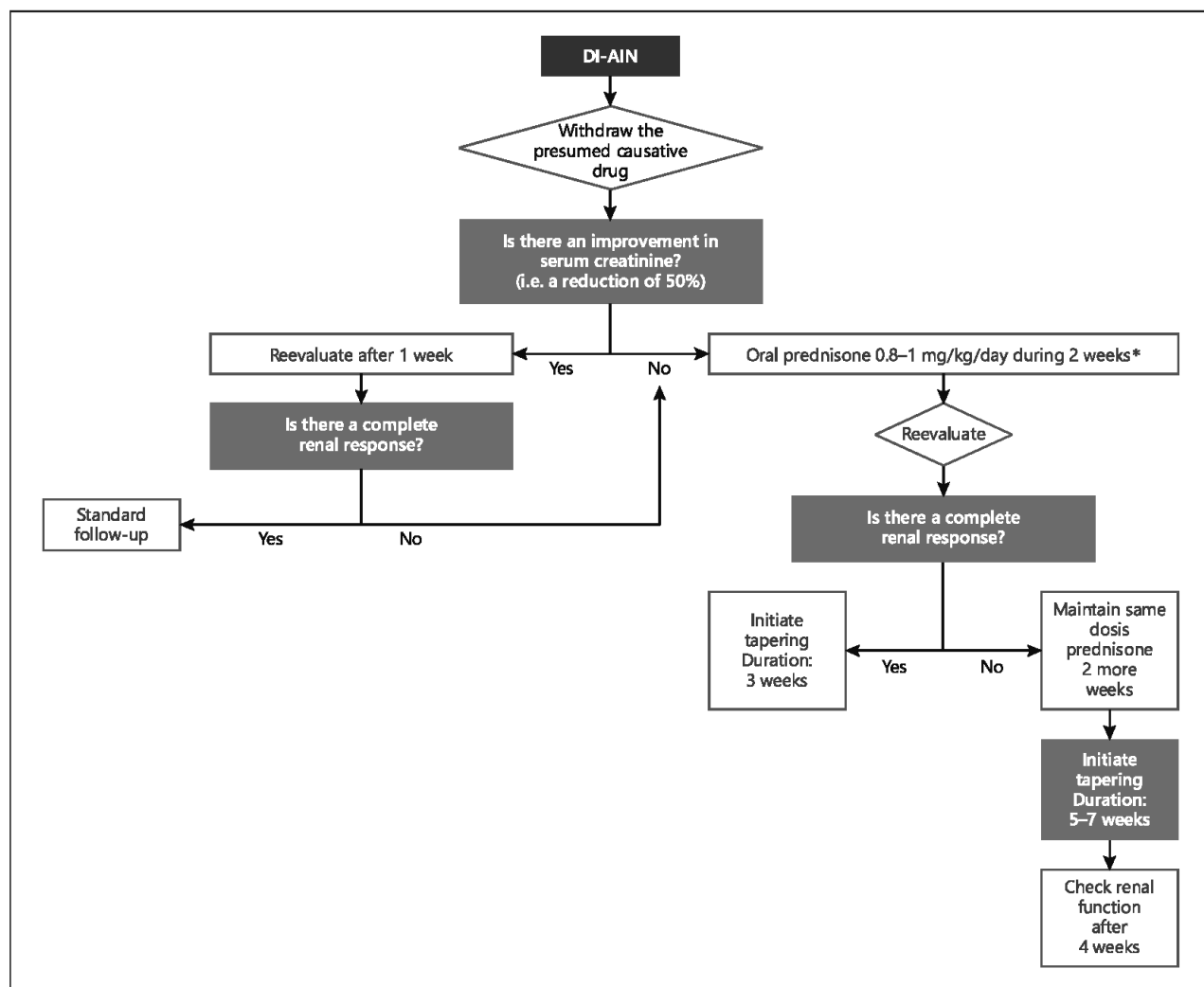


Fig. 2. Proposed treatment algorithm for DI-AIN. The mainstay for the treatment of DI-AIN is the withdrawal of the suspected medication. We recommend reevaluating serum creatinine after a week. In case there is not a significant improvement, we suggest starting treatment with oral prednisolone 0.8–1 mg/kg during 2

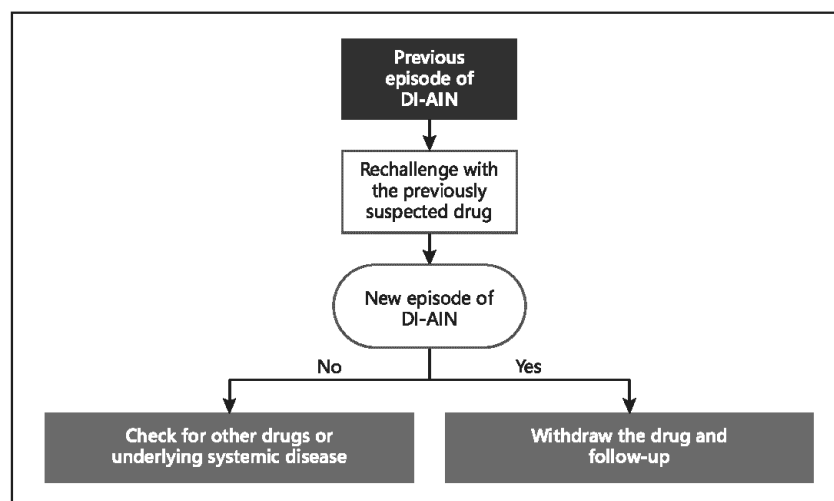
weeks. Once there is a complete renal response, we advocate to initiate steroid tapering, whereas in case of an incomplete response, we suggest to maintain the same dose of prednisone 2 more weeks and then to initiate tapering, which should last 5–7 weeks.

ly corticosteroids would reduce the inflammatory infiltrates of the kidney interstitium, thus preventing the risk of subsequent fibrosis. In moderate-to-severe cases of AIN, the period from the withdrawal of the drug to the start of corticosteroids treatment could even be shorter.

Clarkson and colleagues [48] published a retrospective study on 60 patients diagnosed with AIN (92% DI-AIN), although clinical follow-up data were only available in 42 patients. They found no difference in kidney function at 6 and 12 months of follow-up between patients treated

with corticosteroids (60%) and those who merely received supportive treatment (40%) [48]. The Madrid Interstitial Nephritis Group studied 61 patients with kidney-biopsy-proven DI-AIN. Most patients received corticosteroids (85%). After a mean follow-up of 19 months, kidney function showed a greater improvement in those treated (final serum creatinine 2.1 mg/dL (range 0.7–12.7) compared to those not treated (final serum creatinine 3.7 mg/dL (range 0.7–8.9) ($p < 0.05$), and the number of patients who required kidney replacement therapy was

Fig. 3. Relapses. Some of the patients who have suffered an episode of DI-AIN must face a re-exposure to the drug that had previously been suspected as a culprit of the disease. If the patient suffers a new episode of DI-AIN, the drug should be withdrawn but if there is no new episode, it is necessary to test other drugs.



significantly lower (3.8% vs. 44.4%, p value <0.001) [27]. Interestingly, in this study, there was a significant correlation between the delay in the onset of corticosteroid treatment after drug withdrawal and the final kidney function ($r = 0.45$, $p < 0.005$). Specifically, the benefit was greatest for patients, who received early treatment with steroids, in particular during the first week after stopping the causative drug.

Later studies showed similar findings. In the study conducted by Muriithi et al. [25], 86% of the patients received steroids, and the rest of patients received conservative treatment. After 6 months, serum creatinine in both groups was similar (1.4 vs. 1.5 mg/dL). An interesting observation in this study is the fact that patients achieving partial or complete remission started corticosteroid treatment earlier (at 8 and 11 days, respectively), whereas patients not attaining remission commenced treatment considerably later (at 35 days) (p value = 0.05) [25].

In view of the published results, the following studies have focused on the question of when it is optimal to introduce corticosteroids. This controversy has been addressed in a study including 182 patients with biopsy-proven cases of DI-AIN treated with corticosteroids. Those patients starting treatment with corticosteroids during the first 2 weeks showed better kidney outcomes. In contrast, treatment started beyond 4 weeks exhibited little benefit on the final kidney function. More in detail, the mean time to start corticosteroid treatment was 9 days in the group that had complete recovery, 12 days in the group that had partial recovery, and 29 days in the group that had no recovery (p value = 0.008) [28].

On the other hand, the length of the therapy is not a trivial matter because the use of corticosteroids might produce a wide range of adverse effects. Therefore, a strict balance of the dose and the duration of the treatment must be considered to avoid administering more doses for longer than necessary. Despite its importance, the duration of the treatment with corticosteroids has not been discussed in depth. The study conducted by Fernandez-Juarez et al. [28], discussed the length of the duration of the treatment, concluding that the greatest kidney function recovery was obtained when the entire treatment lasted 8 weeks at maximum, out of which, 3 weeks would correspond to high-dose corticosteroids therapy followed by a tapering period of up to 5–6 weeks.

In conclusion, treatment of AIN remains a challenge since evidence in the literature comes mainly from retrospective studies. The first step in the treatment of DI-AIN is to remove the causative agent of the disease; however, there is evidence on the use of corticosteroids for the treatment of this entity when started rapidly. Therapy should not exceed a total duration of 8 weeks maximum, of which 3 weeks would correspond to high doses of corticosteroids followed by a tapering period of up to 5–6 weeks (Fig. 3).

The treatment alternatives for these patients are not yet standardized. In fact, there is not enough evidence in the literature that encourages the use of other immunosuppressive agents. Clinical cases treated with other immunosuppressive agents, such as cyclophosphamide, cyclosporine, or mycophenolate, are scarce in the literature [65, 66]. In this setting, a recent report of 8 patients with

corticosteroid dependency and recurrent AIN documented an interesting beneficial effect of mycophenolate mofetil.

Prognosis

The initial reports of D-AIN related to methicillin suggested that this entity was a relatively benign disease with a favorable prognosis. Nevertheless, this is far from reality because almost 40% of the patients suffering DI-AIN will experience an incomplete renal recovery with some degree of CKD [15], and around one-third of the patients will require dialysis [45]. The elderly, in addition to being at greater risk for the disease, also have a worse prognosis and usually have more severe kidney failure even requiring hemodialysis [4].

Approximately 2% of all CKD is considered to be due to AIN, which is equivalent to 10 million prevalent worldwide cases. Furthermore, AIN is the primary cause of ESRD in 3–4% of all the cases [67]. It is one of the few potentially treatable causes of AKI if identified and treated early [68]. However, delayed or missed AIN diagnosis leads to ongoing inflammation, resulting in interstitial fibrosis, tubular atrophy, and permanent kidney damage, which may be the explanation for CKD occurring in 40–60% of patients after an episode of AIN [25, 61].

The discovery of a DI-AIN biomarker would be a fundamental finding in order to establish an early and definite diagnosis. Several novel biomarkers have been evaluated as potential diagnostic and prognostic tools. Some studies have highlighted the role of MCP-1, KIM-1, IL-9, and sC5b-9 as possible biomarkers of the disease. Diagnostic techniques have also been developed, such as the lymphocyte transformation test, which measures the proliferation of lymphocytes in the presence of a drug. For example, in one case, a patient developed DI-AIN in the setting of the treatment with nivolumab and lansoprazole [44]. The LTT demonstrated reactivity against lansoprazole and not against nivolumab, indicating which was the culprit drug [24, 59, 60, 69].

Despite different attempts, much remained to be done in order to elucidate the prognostic factors of DI-AIN. So far, any clinical or histological factors have been shown to have an impact on the prognosis. Some authors have tried to correlate the extent of interstitial infiltrates, the severity of tubulitis, the extent of fibrosis, or the presence of granulomas with the outcome of the disease with despair results [6, 15]. The fact that fibrosis and chronic tubular damage is patchy may justify this lack of correlation [25, 70].

Relapses and Refractory Disease

Recurrent AIN is a rare condition, which is associated with worse prognosis and renal survival. In a Spanish study, 22 out of 205 patients diagnosed with DI-AIN presented a clinical relapse after the drug withdrawal. Twenty-seven percent of them had the causative drug reintroduced before the relapse, and 41% of these patients had an undiagnosed autoimmune disease underneath, with a previous wrong diagnosis of DI-AIN. In this study, only the presence of microhematuria, at the time of diagnosis, was more frequently seen in those with an underlying systemic disease.

The treatment landscape for patients with relapses is not standardized. In fact, there is not enough evidence in the literature supporting the use of other immunosuppressive agents than corticosteroids.

In case of refractory disease, it is highly recommended to identify if there is another putative cause, rather than the suspected drug, for example, an underlying disease (Fig. 3). It is also important to mention that when chronic kidney damage is already established and the acute infiltrate has already given way to chronic infiltrate and tubulointerstitial fibrosis, the damage is no longer reversible, and therefore, kidney recovery could not be possible. Thus, corticosteroids should be avoided in those with advanced fibrosis.

Faieta and colleagues [71], reported one case of refractory ICI-induced AIN successfully treated with mycophenolate mofetil. The patient was diagnosed with DI-AIN related to nivolumab, which is a PD-1 inhibitor, in the context of the treatment of a metastatic clear-cell renal-cell carcinoma. The patient was initially treated with corticosteroids for this condition but suffered three relapses. Finally, therapy with pulse 500 mg IV methylprednisolone and 1 daily gram of mycophenolate mofetil was initiated, and the patient recovered kidney function [71].

Conclusion

DI-AIN is an increasingly common entity in clinical practice and an increasing cause of AKI. Its diagnosis remains a challenge for clinicians, due to the nonspecific clinical manifestations and because it can be produced by a myriad of drugs. Certainly, this makes it extremely difficult to identify the causative agent due to polypharmacy in patients and in other cases because it is difficult to control the use of over-the-counter drugs.

So far, the optimal treatment of this entity is not well characterized because there are no clinical trials that provide the highest level of evidence. However, it is considered that the fundamental pillar of treatment consists in the withdrawal of the drug, and if an early recovery of the baseline kidney function is not obtained, treatment with corticosteroids might hasten the recovery of kidney function, and these drugs should be started as soon as possible.

Author Contributions

Conceptualization: Gema Fernandez-Juarez and Beatriz Sanchez-Alamo; methodology: Gema Fernandez-Juarez; literature review: Clara Cases-Corona and Beatriz Sanchez-Alamo; writing – original draft: Beatriz Sanchez-Alamo and Clara Cases-Corona; writing – review and editing: Beatriz Sanchez-Alamo and Gema Fernandez-Juarez; visualization: Beatriz Sanchez-Alamo and Gema Fernandez-Juarez; and supervision: Gema Fernandez-Juarez.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Data Availability Statement

All articles analyzed during this review are included in the references. Further inquiries can be directed to the corresponding author.

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Review Article

Acute kidney injury associated with non-steroidal anti-inflammatory drugs

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ABSTRACT

Non-steroidal anti-inflammatory drugs (NSAIDs) are ones of the commonly prescribed drugs worldwide. They primarily inhibit cyclooxygenase (COX) enzyme which is responsible for conversion of phospholipids to various prostaglandins (PGs). Disruption in PGs production affects the kidneys in several ways, including vasoconstriction that may result in ischemic acute kidney injury (AKI) in at-risk patients. They also impair salt and water excretion, leading to edema and hypertension. Other complications include hyperkalemia, hyponatremia, nephrotic syndrome, acute interstitial nephritis and chronic kidney disease progression. AKI from NSAIDs is usually reversible with favorable prognosis after discontinuation of NSAIDs. Avoidance of NSAIDs exposure is extremely important, especially among high-risk patients.

1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly prescribed drugs that are accounted for 5–10% of all prescriptions in the United States. [1] Acetyl salicylic acid (ASA) is the first agent that was discovered in 1893. [2] Since then, many agents have been developed and widely used for various conditions. NSAIDs exert their anti-inflammatory effect via cyclooxygenase (COX) inhibition. Their common adverse effects include gastrointestinal ulcers, cardiac toxicity, bleeding diathesis, allergic reaction and renal complications, [3,4] with acute kidney injury (AKI) being the most common form of NSAIDs-induced renal injury. Other renal manifestations include hypertension, edema, hyponatremia, hyperkalemia, nephrotic syndrome, papillary necrosis and interstitial nephritis. [5] In addition, several studies have demonstrated a relationship between exposure to high dose NSAIDs and progression to advanced stage chronic kidney disease (CKD) [6]. Unfortunately, despite the well-established adverse effects, the frequency of NSAIDs utilization among high risk patients, such as those with heart failure, hypertension and CKD, remains high. [7] A study of kidney transplant recipients demonstrated that 11% of them were prescribed NSAIDs, in which about two-third of the prescriptions were from primary care physicians and less than 50% had appropriate laboratory monitoring. [8]

The purpose of our review is to summarize the current evidence on mechanism of action of NSAIDs and their effects on the kidneys. We also provide detailed information on each renal complication with a focus on clinical presentation, treatment and outcome.

1.1. Mechanism of action of NSAIDs

NSAIDs inhibit cyclooxygenase (COX) which is also known as prostaglandin H synthase. [9] There are two distinct isoforms of COX: COX-1 and COX-2. COX-1 is ubiquitous and constitutively expresses in normal cells. On the other hand, COX-2 is largely upregulated in inflammatory state. [10] However, several studies have demonstrated an expression of COX-2 during normal state in several organs such as brain, reproductive organs and kidneys. [11] The two isoforms of COX are 60% identical and located at luminal compartment of endoplasmic reticulum and nuclear membrane. [9] NSAIDs bind with COX-1 via reversible hydrogen bond whereas the binding of COX-2 is an irreversible active process. [12] COX enzyme primarily involves in eicosanoid biosynthesis which converts arachidonic acid to prostaglandin (PG) G₂. PGG₂ is then converted to PGH₂ via peroxidase enzyme. [13] Ultimately, PGH₂ is metabolized to various types of PG including PGE₂, PGF_{2α}, PGI₂ and thromboxane (TX) A₂ via isomerase enzymes (Fig. 1). [2] NSAIDs exert their anti-inflammatory property mainly via COX-2 inhibition whereas COX-1

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inhibition often results in adverse effects. NSAIDs can be classified based on their COX-2 selectivity: non-selective COX inhibitors and selective COX-2 inhibitors. [11] NSAIDs can also be classified based on their chemical structure and property such as carboxylic acids, acetic acids and propionic acids.

1.2. Pathophysiology of NSAIDs-induced acute kidney injury

NSAIDs primarily incite AKI via hemodynamic alteration from prostaglandins imbalance. [14] As previously mentioned, COX-1 is generally expressed in the kidneys during non-inflammatory state. Additionally, low level of COX-2 expression can be found in macula densa. [15] PGs are expressed in several parts of nephron, including glomeruli, juxtaglomerular apparatus (JGA), loop of Henle, interstitial and tubular cells. Their function and site-specific expression help maintaining and modulating renal function (Fig. 1).

PGI₂ (Prostacyclin) is up-regulated by vasoconstrictive hormones such as angiotensin II, vasopressin, endothelin and norepinephrine. Various injuries, including renal ischemia and autoimmune process in renal parenchyma, can stimulate PGI₂ production. [16] Its receptors are located at glomerular mesangial cells, endothelial cells and podocytes. [17] It enhances arteriolar vasodilation, decrease vasopressin and increase sodium excretion, thus promote diuresis. It can also attenuate podocytes contraction and inhibit leukocyte adhesion and aggregation. [18]

PGE₂ is expressed in all type of renal cells but mostly in glomeruli and collecting ducts. There are three types of PGE₂ synthase, including microsomal PGE synthase (mPGES)-1, mPGES-2 and cytosolic PGE synthase. PGE₂ binds to EP receptor which has 4 subtypes (EP₁-EP₄).

[19] EP₁/EP₃ act as vasoconstrictor whereas EP₂/EP₄ act as vasodilator of afferent arterioles. EP₂/EP₄ also serve as vasodilator for vasa recta. It is a mediator of renin-angiotensin aldosterone synthesis (RAAS) that can stimulate renin release via EP₃ from the macula densa. [19] Overall, PGE₂ promotes vasodilation, natriuresis and aquaresis. [5]

TXA₂ is widely expressed and can be found in macrophages, lung, peritoneum and kidneys. Expression of TXA₂ particularly abundant in platelet which promotes platelet activation and aggregation. [20] In the kidneys, TXA₂ is primarily expressed in glomeruli. It promotes vasoconstriction and podocytes contraction, thus decrease renal blood flow and glomerular filtration (GFR) [6].

PGF_{2α} is converted from PGD₂ via 11-ketoreductase. It is highly expressed along genitourinary tract, including ovaries and kidneys. [21] Distal convoluted tubule and cortical collecting duct are the main sites of renal expression. It promotes sodium and water excretion via trans-cellular transport of sodium independently of blood pressure and GFR. [6,22] It also stimulates thiazide-sensitive Na-Cl- cotransporter in distal convoluted tubule. [23]

NSAIDs deplete locally produced PGs in the kidneys and, thus, blunt vasodilatory and other compensatory effects. These effects are especially crucial for high-risk patients who already have up-regulated RAAS and vasoconstrictive mediators (endothelin-1 (ET-1) and norepinephrine) as they are dependent on vasodilation properties of PGs to maintain normal renal hemodynamics. PGI₂ and PGE₂ are the main vasodilators. PGI₂ enhances afferent, efferent and capillary tuft dilatation. PGE₂ also dilates afferent arterioles. [24] Removal of vasodilators can impose unopposed severe renal vasoconstriction. Ultimately, this may lead to irreversible renal ischemia and acute tubular necrosis. [25] Several animal studies have shown that prostacyclin reduction increases risk of

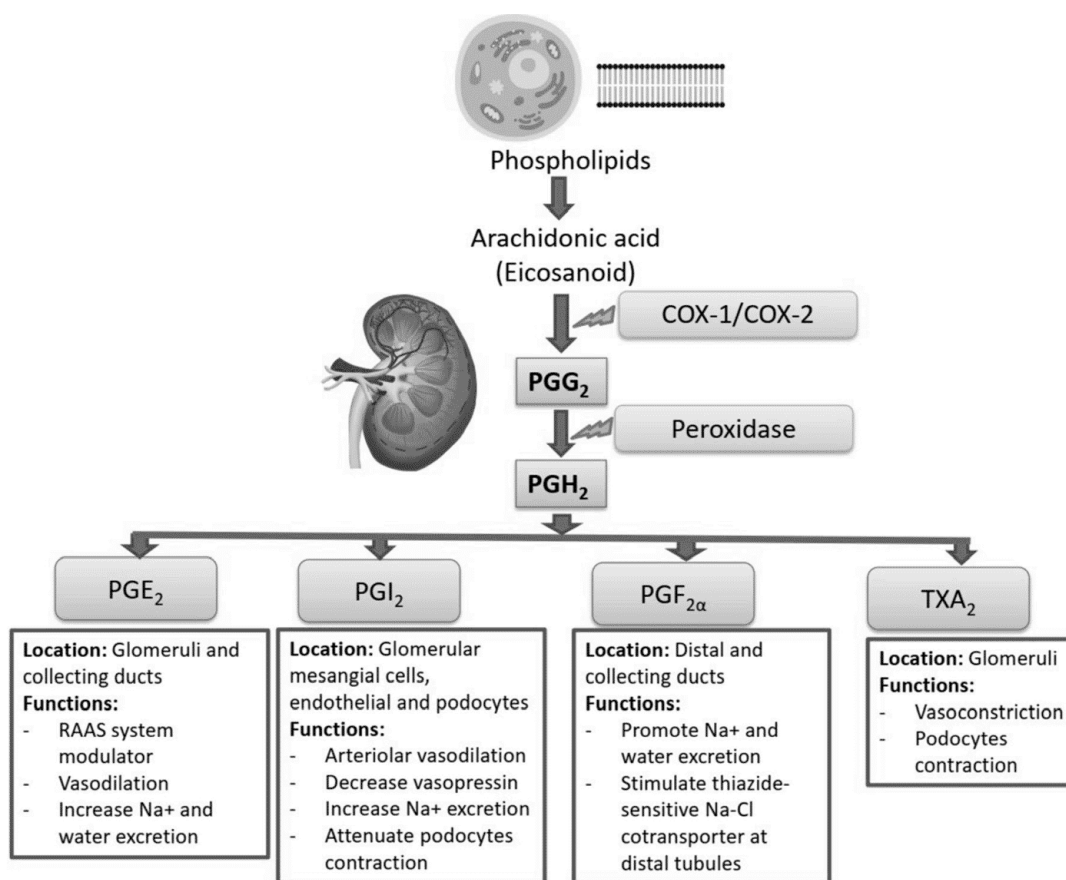


Fig. 1. Prostaglandins production cascade, locations and their functions. Abbreviations: PG, prostaglandin; TXA₂, thromboxane A₂.

ischemic kidney injury [26] and endothelial PGs could protect kidneys from ischemic insult. [18] These studies confirm the inhibitory role of NSAIDs in PGs production leading to ischemic injury (Fig. 2).

1.3. Risk factors for AKI in NSIADs user

NSAIDs associated AKI typically occurs in patients with pre-existing compromised kidney hemodynamics [27]. Studies have shown that NSAIDs do not alter kidney functions in otherwise healthy people. There are several risk factors as summarized in Fig. 2. Patients are characteristically dependent on vasodilatory effect of renal prostaglandins to maintain renal blood flow and GFR. This typically occurs in patients with RAAS activation, such as those with heart failure, liver cirrhosis, nephrotic syndrome and volume depletion [5,28]. In a case series of pediatric patients without significant underlying medical conditions, all patients with NSAIDs associated AKI had a history of volume loss [29]. A salient study of patients with severe congestive heart failure has demonstrated RAAS activation along with systemic upregulation of PGI₂ and PGE₂, suggesting the importance of vasodilatory effect of PGs in these patients [30].

Other risk factors include older age, male gender, hypertension, diabetes, CKD and concomitant use of nephrotoxic agents [24,31]. The risk of AKI is doubled in older population [32]. Nonetheless, NSAIDs can increase risk of AKI in pediatric population who are at risk for volume depletion [33,34]. Kidney transplant recipients are also at higher risk of NSAIDs associated AKI with the risk of almost three times higher than in native kidneys [35].

Selective COX-2 inhibitors were previously thought to have less renal effect due to the specificity toward COX-2. However, subsequent studies demonstrated that both traditional NSAIDs and selective COX-2 inhibitors can enhance the risk of AKI although the association of selective

COX-2 inhibitors and AKI may not be as strong as traditional NSAIDs [36,37]. A retrospective cohort study demonstrated that selective COX-2 inhibitors use was associated with rapid eGFR decline in both short term (<1 year) and intermediate term (1–2 year) among CKD patients and eGFR continued to decline after NSAIDs discontinuation [38]. However, a recent meta-analysis did not display a significant association between AKI and selective COX-2 inhibitors [37]. Among traditional NSAIDs, indomethacin may confer the highest risk of AKI compared to other NSAIDs [37].

NSIADs users who are on concomitant diuretic and RAAS inhibitor (RAASI) have 30–60% increased risk of AKI which is higher than the risk of AKI from NSIADs alone or NSIADs with either diuretics or RAASI. [39, 40] The risk is at the highest within one month of initiation [40]. Notably, the risk of AKI in concomitant users advances as the age increases [39]. Due to its high AKI risk, patients who use of NSAIDs, diuretics and RAASI concomitantly is typically known as the “triple whammy”. In this circumstance, there is an overwhelming disruption of renal autoregulation, resulting in a drastic reduction in GFR and ischemic insult [41]. Other medications that appears to heighten the risk of AKI when used in conjunction with NSAIDs include acyclovir, valacyclovir, tenofovir and proton-pump inhibitor [42,43].

2. Clinical presentation

Renal manifestation of NSAIDs is protean, including fluid retention leading to edema, hypertension, hyperkalemia, AKI, nephrotic syndrome, papillary necrosis and interstitial nephritis [28]. Clinicians should be aware of these manifestations and promptly ask for history NSAIDs exposure. These manifestations are demonstrated in Fig. 3.

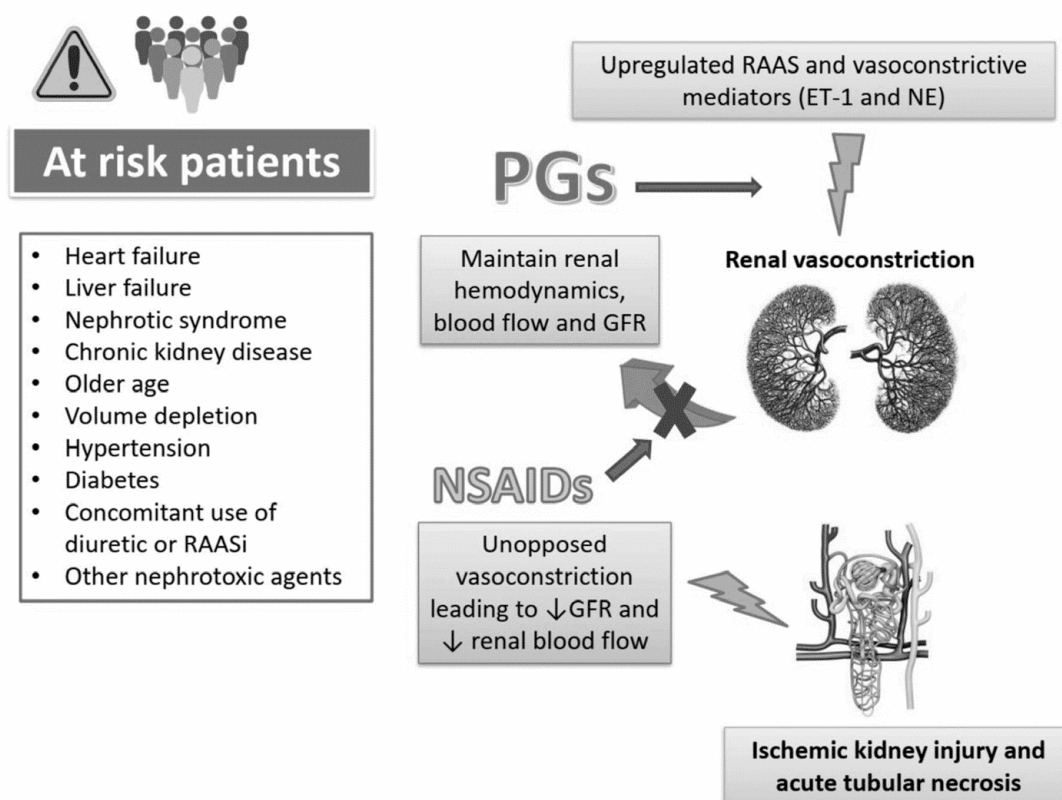


Fig. 2. Risk factors of NSAIDs induced nephrotoxicity and mechanism of acute kidney injury. Abbreviations: RAASI, renin angiotensin aldosterone system inhibitor; PGs, prostaglandins; NSAIDs, nonsteroidal anti-inflammatory drugs; ET-1, endothelin-1; NE, norepinephrine.

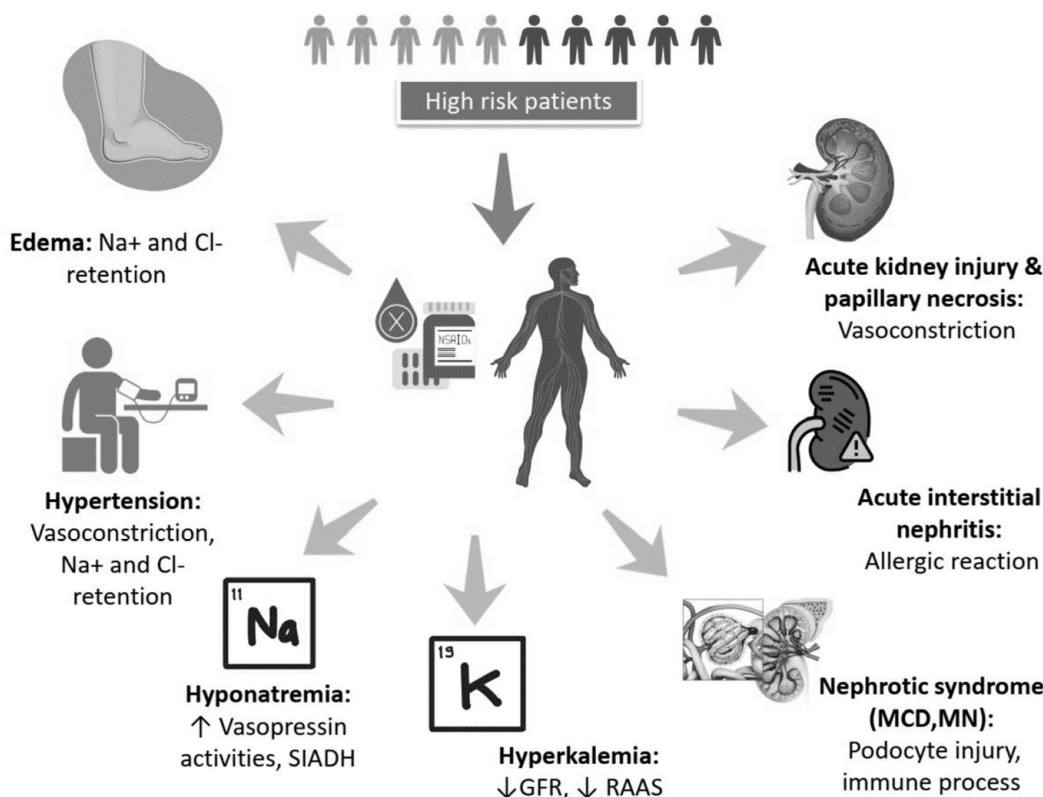


Fig. 3. Spectrum of NSAIDs induced nephrotoxicity. Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; SIADH, syndrome of inappropriate anti-diuretic hormone; GFR, glomerular filtration rate; RAAS, renin angiotensin aldosterone system; MCD, minimal change disease; MN, membranous nephropathy.

2.1. Hypertension

NSAIDs have been shown to elevate blood pressure in both normotensive and hypertensive patients [44]. Earlier studies have shown that indomethacin, naproxen and piroxicam have the greatest effect on blood pressure whereas the least effect is observed in sulindac [44–46]. However, recent studies including a double-blind, randomized multicenter trial have shown that ibuprofen is harboring the greatest effect on blood pressure compared to non-selective and selective COX-2 inhibitors [47]. In fact, COX-2 inhibitors minimally affect BP with only 2.3% blood pressure increase during the use [47]. In general, blood pressure can be increased by 2–5 mmHg in NSAIDs user [44,46]. In hypertensive patients, patients who receive beta-adrenergic antagonist appear to have the highest increase in blood pressure after exposure to NSAIDs compared to those who receive other anti-hypertensive agents [46]. There are several possible mechanisms that can explain the rise of blood pressure, including AKI, vasoconstriction, salt and water retention and vascular endothelial dysfunction [44,47].

2.2. Edema

The incidence of NSAIDs-induced edema is fairly low (<10%) [48]. Patients may have 0.5–1 kg weight gain as a result of NSAIDs exposure [49]. Prostaglandin deficiency (particularly PGE₂) induces reduction in renal blood flow and GFR [48]. It enhances Na⁺ and Cl⁻ reabsorption via Loops of Henle and up-regulation of vasopressin. Lastly, it can up-regulate endothelin-1 which, in turn, promotes Na⁺ and Cl⁻ reabsorption. All of these would ultimately result in salt and water retention and edema [44,50].

2.3. Hyponatremia

NSAIDs associated symptomatic hyponatremia is rare [49]. It often occurs in patients with other risk factors of hyponatremia, such as heart failure, cirrhosis, hypovolemia and thiazide diuretic use [6,51,52]. NSAIDs can induce hyponatremia via several mechanisms. They block the PGE₂ inhibitory effect of vasopressin-activated adenylate cyclase in collecting duct, resulting in up-regulation of vasopressin activity [49]. There are several case reports that concomitant use of NSAIDs and desmopressin can generate severe hyponatremia [53,54]. NSAIDs use in marathon runner and other athletes also increases risk of hyponatremia during their performance. In a study of 28 marathon runners, there was a reduction of serum sodium in NSAIDs user whereas serum sodium was increased in non-NSAIDs users [55]. Vasopressin level was noted to be higher in hyponatremic athletes compared to normonatremic group [56]. Hence, potentiation of vasopressin via NSAIDs may explain the observed elevated risk. NSAIDs can reduce medullary blood flow thus increase hypertonicity of medullary interstitium and promotes water absorption [49]. There are also case reports of syndrome of inappropriate antidiuretic hormone (SIADH) after exposure to different NSAIDs, including ibuprofen, indomethacin, piroxicam, sulindac, diclofenac and ketorolac. [57–59] However, other vasopressin stimuli often co-existed with NSAIDs use in these reports [6,58]. Moderate to severe hyponatremia is associated with an increased risk of in-hospital mortality [60].

2.4. Hyperkalemia

PGs can promote renal blood flow, resulting in increased GFR and potassium clearance. They also increase distal Na⁺ delivery and promote potassium excretion via distal tubule. Furthermore, PGs secreting from macula densa can enhance renin secretion, aldosterone production

and increase kaliuresis [5]. These mechanisms are compromised in NSAIDs users, resulting in diminished potassium clearance. Typically, serum potassium rises by 0.2–0.6 mEq/L. Nonetheless, life-threatening hyperkalemia has been reported [61]. Patients with CKD, diabetes and concomitant RAASi use are at increased risk of hyperkalemia [31,49,62]. Risk of hyperkalemia varies by type of NSAIDs and both non-selective and selective COX-2 inhibitors can cause hyperkalemia [38,63].

2.5. Acute kidney injury

NSAIDs associated AKI does not often frequently in otherwise healthy person. Studies have demonstrated modest increased risk of AKI in the community setting with OR ranging between 1.5 to 2.1 [32,37]. AKI could be seen as early as 1–3 days after exposure depending on NSAIDs half-life [5]. Patients usually present with mild to moderate rise in creatinine and minimal proteinuria although dialysis may be required in rare instances [29]. Renal pathology typically reveals evidence of tubular injury with vacuolated and loss of brush border, leading to simplification of tubular epithelial cells, although biopsy is usually not required in mild to moderate cases [25]. Inflammatory cells infiltration may present [25,64]. In severe case, bilateral renal infarctions may occur [65]. There are also case reports of NSAIDs-induced AKI via massive rhabdomyolysis [66]. Renal function usually improves within 2–7 days after NSAIDs withdrawal [5] and other conservative management, such as fluid resuscitation. [29] However, permanent kidney damages may occur, particularly in patients with more chronic use.

2.6. Acute interstitial nephritis (AIN)

AIN is characterized by inflammatory cell infiltration in tubulointerstitial compartment. Patients often present with AKI and some may have other systemic symptom such as rash, arthralgia, fever and peripheral eosinophilia [67]. Of all AIN cases, drug-induced AIN accounts for more than two-third and NSAIDs are ones of the most common culprits [67]. Renal pathology usually shows cytotoxic T-cell with a paucity of eosinophils, which is notably different from classic AIN from other medications [68]. The median age of patients with NSAIDs induced AIN is around 50 years. Patients with NSAIDs induced AIN may concomitantly develop nephrotic syndrome but frequently have sub-nephrotic range proteinuria with median urine protein of 1.1 g/d [69]. About two third of patients developed AKI stage 3 with median peak serum creatinine of 3.6 mg/dl. The median time of exposure is 3 months before the diagnosis. Patients often respond well to steroid therapy and 70% have improved kidney function to near normal [69]. Some studies suggest that early steroid treatment is associated with better outcome [70].

2.7. Nephrotic syndrome

Nephrotic syndrome may occur in NSAIDs users irrespective of their baseline kidney function [28]. It usually occurs between 2 weeks and 18 months after exposure [28]. Minimal change disease (MCD) and membranous nephropathy (MN) are previously thought to be the two most common nephrotic syndromes associated with NSAIDs use [71]. However, a recent large cohort study from the UK has found that membranous nephropathy (39%), focal and segmental glomerulosclerosis (FSGS) (20%) and diffuse crescentic glomerulonephritis (11%) were actually more common than minimal change disease (9%). Nonetheless, it should be noted that only 10% of patients in this cohort underwent a kidney biopsy [72]. They also found that past NSAIDs use (between 2 months and 2 years) as well as current use (2 to 4 weeks) increased odds of nephrotic syndrome with the ORs of 1.24 (1.07–1.43) and 1.34 (1.06–1.70), respectively [72]. Acetic acid derivatives (aspirin) and propionic acid derivatives (ibuprofen, naproxen and fenoprofen) are associated with higher odds [72]. Tip lesion FSGS is also reported in an

NSAIDs user [73]. Pathophysiology of NSAID induced nephrotic syndrome remains unclear but it has been postulated that NSAIDs can induce podocyte injury which may incite immune process leading to autoantibodies production [74].

MCD secondary to NSAIDs is often accompanied by severe AKI and may occur with or without concurrent interstitial nephritis [75–77]. Kidney pathology typically demonstrates minimal changes under light microscopy and diffuse foot process effacement under electron microscopy [76]. Treatment involves NSAIDs discontinuation and immunosuppression. Prognosis is generally favorable.

MN is the most common cause of nephrotic syndrome in adults [78]. Prior to the discovery of phospholipase A2 receptor antibody, it has been categorized as primary and secondary MN (in which drug-induced MN belongs to) [79]. Kidney pathology usually reveals mesangial expansion with thickened basement membrane with immunofluorescence displaying IgG granular capillary loop staining. IgG subclass may aid in differentiating primary and secondary MN. Primary MN predominantly has IgG4 deposition whereas secondary MN (such as NSAIDs-induced MN) frequently has IgG1 deposition [74]. However, antigen identification of immune deposits may now become more clinically relevant than the IgG subclass [80]. A study of NSAIDs-induced MN reported the mean age of 55 years old with median onset of 43 weeks (range from 4 weeks to 3 years) after exposure. Most patients had massive proteinuria with mean proteinuria of 10.2 g/day but none required dialysis. Proteinuria usually improved after drug cessation and conservative management without immunosuppression, which is different from primary MN that usually required immunosuppressive treatment [81]. Re-introduction of NSAIDs may result in a relapse of MN [74].

2.8. Papillary necrosis (PN)

PN is a rare kidney disease with reported prevalence of 0.1% and 3–5% in non-diabetic and diabetic patients, respectively, [82] although the prevalence can be as high as 20% in an autopsy series [83]. Risk factors include prolonged NSAIDs use, diabetes mellitus and sickle cell anemia [84,85]. Patients can present with non-specific symptoms such as nocturia, dysuria, pyuria, microscopic hematuria, proteinuria and ureteral colic [86]. Some patients may develop back pain and passing sloughed papillae in the urine [85]. In a severe case, necrotic papillae can clog up ureter resulting in bilateral ureteral obstruction [87]. Kidney imaging may demonstrate calyceal haziness or failure of contrast media filling of minor calyces [86]. Kidney pathology typically reveals coagulative necrosis at renal papilla. Fibrosis and calcification are common in chronic cases [85]. Several animal studies have confirmed the role of NSAIDs in its pathogenesis [88–90]. The anatomical vascular bundles of papillary vessels that only a single or few vessels supplying renal papillae results in over dependency of local PGs in maintaining blood flow to the papillary tip. Therefore, papillary tip is especially vulnerable to severe ischemia in the setting of PGs depletion from NSAIDs [86]. Renal outcome is favorable in PN with less than 2% required dialysis upon diagnosis and 6% during the follow-up period [91].

2.9. Chronic kidney disease progression

The association between NSAIDs use and risk of CKD has not been well-established as earlier studies that demonstrated an enhanced risk of CKD among NSAIDs users suffered from several biases and methodological flaws [92,93]. Nonetheless, more recent studies with better quality appear to show the same result. In a community study, NSAIDs users have a higher odds of developing CKD with OR of 1.63 (95% CI 1.22–2.19) [32]. They are also at increased risk of CKD progression, particularly among high dose users, with the pooled OR 1.26 (95% CI 1.06–1.50) [94,95]. The risk appears to be especially heightened among those with history of hypertension and diabetes [96,97]. Unfortunately, NSAIDs are still prescribed in majority of CKD patients. A recent cross-sectional study showed that nearly two-third of CKD patients were

prescribed NSAIDs and 80% of them were regular users [98].

2.10. Renal cell carcinoma (RCC)

Kidney cancer is one of the most common cancers in the United States with RCC being the most common type accounting for 85% of cases. Studies have suggested that non-aspirin NSAIDs may increase the risk of RCC [99–102]. A recent meta-analysis found that non-aspirin NSAIDs users had a higher risk of incident RCC with the pooled relative risk of 1.25 (95% CI 1.06–1.46). A dose-response relationship was also observed [103]. The pathophysiology remains unclear but may be related to chronic kidney injury leading to DNA damage and carcinogenesis [102].

2.11. Treatment and outcomes

Discontinuation of NSAIDs along with conservative management is generally sufficient for management of renal complications from these drugs. More importantly, avoidance of NSAIDs is crucial especially in high-risk patients. In patients with mild CKD (stage 1–3), only short-term use (≤ 5 days) with close monitoring is allowed. [6] In CKD stage 4, if it is felt to be necessary and no other alternative agents, short-term and low dose NSAIDs may be considered but with close monitoring for renal toxicity. NSAIDs should be avoided in stage 5 CKD due to high risk of renal complications [6]. AKI secondary to NSAIDs use is typically reversible after discontinuation with a favorable prognosis. Similarly, patients with nephrotic syndrome (MN and MCD) usually respond to NSAIDs withdrawal along with conservative management. However, some patients may require immunosuppression particularly in severe and refractory cases. Similarly, patients with AIN typically responds to NSAIDs discontinuation but often require short course of steroid to ameliorate the inflammation.

3. Conclusion

NSAIDs are ones of the most common prescribed drugs worldwide. They exert their anti-inflammatory action via COX inhibition leading to PGs imbalance. PGs depletion subsequently induces vasoconstriction and impairment of salt and water excretory function. Patients with CKD and upregulated RAAS (heart failure, liver failure or volume depletion) are at increased risk of renal toxicity. AKI from ischemic insult is the most common pattern of renal complications. Hypertension, hyperkalemia, hyponatremia, edema, nephrotic syndrome, AIN and CKD progression are also observed. Discontinuation of NSAIDs along with conservative management is generally sufficient for management of the renal complications. More importantly, avoidance of NSAIDs is crucial especially in high-risk patients.

Financial disclosure

None.

Conflict of Interest

Authors declare no conflict of interest.

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Kidney manifestations of tuberous sclerosis complex

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INTRODUCTION

Tuberous sclerosis complex (TSC) is a genetic disease with autosomal dominant inheritance. (See "Tuberous sclerosis complex: Genetics and pathogenesis", section on 'Genetics'.)

This topic will review the renal manifestations of TSC, which include angiomyolipomas (AMLs), renal cysts, renal cell carcinoma (RCC), and other, less common manifestations. Sporadic renal AMLs and renal AMLs associated with sporadic pulmonary lymphangiomyomatosis (LAM) are discussed elsewhere (see "Renal angiomyolipomas (AMLs): Management"). The clinical features, diagnosis, and management of TSC are also discussed in detail elsewhere. (See "Tuberous sclerosis complex: Clinical features" and "Tuberous sclerosis complex associated lymphangioleiomyomatosis in adults" and "Tuberous sclerosis complex: Management and prognosis".)

GENETICS AND PATHOGENESIS

•**Genetics** – TSC is caused by mutations in either the *TSC1* gene on chromosome 9 or the *TSC2* gene on chromosome 16. The gene product of *TSC1* is hamartin, and the gene product of *TSC2* is tuberin. (See "Tuberous sclerosis complex: Genetics and pathogenesis", section on 'Genetics'.) *TSC2* mutations generally produce a more severe phenotype than *TSC1* mutations [1,2]. This includes a higher frequency and severity of renal angiomyolipomas and renal cysts and a higher risk for the development of renal cell carcinoma (RCC). (See "Tuberous sclerosis complex: Genetics and pathogenesis", section on 'Genotype-phenotype correlations'.)

TSC2 mutations may also be associated with autosomal dominant polycystic kidney disease (PKD) since the *TSC2* gene is adjacent (tail-to-tail) to the *PKD1* gene. Deletions that inactivate both genes are associated with polycystic kidneys that are most often diagnosed during the first year of life or early childhood; this disorder is called the *TSC2/PKD1* contiguous gene syndrome. By contrast, somatic mosaicism, which is well documented in TSC, can greatly attenuate both phenotypic manifestations and severity of the disease [3]. This condition is due to a TSC mutation acquired by one of multiple pluripotent stem cells during early embryogenesis and is increasingly recognized in TSC patients with no detectable mutations using next-generation sequencing [4]. (See 'TSC2/PKD1 contiguous gene syndrome' below and 'Autosomal dominant polycystic kidney disease (ADPKD): Genetics of the disease and mechanisms of cyst growth', section on 'Genetics'.)

The prevalence of renal lesions in TSC increases with age, eventually affecting up to 80 percent of patients [2,5-8].

•**Pathogenesis** — The monogenic cause of TSC is well established, but the pathogenesis of TSC-associated kidney lesions (eg, angiomyolipomas [AML] and cysts) remains incompletely understood [9]. Biallelic *TSC1* or *TSC2* inactivation is sufficient for human AML formation [10,11] but genetic studies of kidney cystic lesions in murine models identified second-hit *TSC1* or *TSC2* mutations in only 30 percent of cysts [12,13], suggesting other mechanism(s) may be involved in cyst formation. The nature of second-hit somatic *TSC1* or *TSC2* mutations in TSC kidney lesions is also complex. Although most such mutations are unique, identical second-hit *TSC1* or *TSC2* mutations have been documented in AMLs and pulmonary TSC (ie, lymphangiomyomatosis [LAM]) within the same patient [14,15]. Two models have been proposed to explain this unusual observation: (1) the “benign metastasizing model” stipulates that AML and LAM lesions arise from a third lesion from an unknown primary site such as the lymphatic system, which metastasizes to both the kidney and lung; or (2) the “developmental mutagenesis model” posits that somatic loss of *TSC1* or *TSC2* in a polypotent stem cell that forms constituents of both the kidney and lung during early embryonic development gives rise to spatially distinct lesions of identical genetics later in life [9]. Finally, the specific cell-of-origin for kidney AML lesions and cysts also remains uncertain. It is possible that cell potency at the time of somatic *TSC1* or *TSC2* mutagenesis is proportional to the complexity of the kidney lesion: specifically, somatic *TSC1* or *TSC2* mutation events that occur later in more specialized cell types may generate less compositionally complex lesions (eg, fat-poor AML) [9].

ANGIOMYOLIPOMAS

Epidemiology — Angiomyolipoma (AML) is the most common renal lesion observed among patients with TSC. In various series, AML have been reported in 75 to 85 percent of TSC patients with renal lesions and in 49 to 60 percent of TSC patients overall [2,5,6] (see 'Genetics and pathogenesis' above). AMLs belong to a family of tumors collectively referred to as "neoplasms with perivascular epithelioid

differentiation," which were previously called "perivascular epithelioid cell tumors" and now are referred to as "PEComas" [16]. These tumors arise by clonal proliferation of epithelioid cells distributed around blood vessels [17] and, in patients with TSC, include renal AMLs and pulmonary lymphangiomyomatosis (LAM). A TSC-associated AML lesion may be due to clonal expansion of pericytes in the kidney that has undergone biallelic (ie, germline plus a somatic) mutations of a TSC gene [18].

Among patients with TSC, the prevalence and size of renal AMLs increase with age [2,5,6,19-25]. Renal AMLs are more numerous and reach a larger size in women than in men, suggesting a hormonal effect on TSC development and growth, which can also occur in prepubertal girls, who have higher estradiol levels than boys [26].

In one study of 164 children with TSC who underwent serial renal ultrasonography or computed tomography (CT), there were no renal AMLs in the first year of life [22,23]. In contrast, renal AMLs were present in 37 percent of the children between one and five years of age and in 41 percent of boys and 63 percent of girls after five years of age. Increasing prevalence with age has been described in older children with TSC. In a longitudinal study of 60 such patients, renal AMLs were present in 48 percent of boys and 60 percent of girls at a mean age of 6.9 years and in 76 percent of boys and 83 percent of girls at follow-up at a mean age of 10.5 years [5]. The overall prevalence of AMLs among patients with TSC is discussed above. (See 'Genetics and pathogenesis' above.)

In addition to the increase in prevalence of renal AMLs, the number and size of renal AMLs also increase with age [2,5,6,24,25].

- In the above series of children with TSC who had follow-up at a mean age of 10.5 years, growth of renal AMLs occurred in 10 of 18 boys (3 an increase in number and 7 an increase in size) and in 18 of 27 girls (17 an increase in number and all 18 an increase in size) [5].
- In a large series from the Netherlands (351 adult TSC patients and 244 with at least one AML ≥ 3.5 cm) in which AML were classified according to size, number, and renal morphology, the median age of patients with no detectable AML > 1 cm was 37 years, whereas the median age with stage 3 (ie, at least one AML ≥ 3.5 cm) was 46 years (table 1) [27].

Cautious interpretation is warranted when considering these ultrasound data, however, because ultrasound often cannot detect fat-poor angiomyolipomata, and approximately a third of patients demonstrate such fat-poor lesions.

Histology — There are two major histologic types of renal AMLs associated with TSC: classic and epithelioid (picture 1) [20,28,29]. (See "Renal angiomyolipomas (AMLs): Management".)

An epithelial component may be more common in patients with TSC than patients with sporadic AML, 27 versus 7 percent in one series [30]. Epithelioid variants may undergo malignant transformation. Although this is infrequent, the relative risk is greater in patients with TSC [30-32].

The histology of AMLs is discussed in detail separately. (See "Renal angiomyolipomas (AMLs): Management".)

Clinical presentation — Although renal involvement is common in TSC, many patients have few or no symptoms related to the kidney disease [8]. Thus, most patients with

TSC-related AML come to attention on surveillance imaging. (See "Tuberous sclerosis complex: Clinical features" and "Tuberous sclerosis complex: Evaluation and diagnosis", section on 'Initial evaluation' and "Tuberous sclerosis complex: Management and prognosis", section on 'Renal disease'.)

Occasionally, patients with TSC present with a renal AML, either because of retroperitoneal hemorrhage, hematuria, or impingement of the AMLs on normal tissue, which can impair renal function.

Following are common clinical presentations:

- Hemorrhage** – The most common clinical manifestations of symptomatic renal AMLs are related to hemorrhage (hematuria, intratumoral, or retroperitoneal hemorrhage) and to their mass effect (abdominal or flank mass, flank pain and/or tenderness, hypertension, and renal insufficiency) [2,20,25,33,34]. The chances of developing symptoms among patients who have an AML is directly related to its size. As a rule, renal AMLs larger than 4 cm are more likely to grow, develop micro- and macroaneurysms, and cause symptoms [20,34]. The International Guidelines for surveillance and management of TSC have recommended that AMLs that are ≥ 3 cm in diameter and enlarging should be treated preemptively [35].

AMLs may cause significant and occasionally life-threatening hemorrhage. Renal AMLs are the most common cause of Wunderlich syndrome, a life-threatening, nontraumatic renal hemorrhage into the subcapsular and perirenal spaces [36]. The risk of significant hemorrhage is related to the degree of vascularity, the AML size, and the size of aneurysms within the AML. Increased vascularity [37] and/or aneurysm size (5 mm or more) [38] are associated with an increased risk of AML rupture. The risk of bleeding may rise during pregnancy, possibly due to rapid growth induced by hormonal changes and/or increased blood volume [39-42].

- Chronic kidney disease (CKD)** – Some patients develop significant renal impairment, including end-stage kidney disease (ESKD), due to destruction of renal tissue related to extensive bilateral renal AMLs. (See 'Chronic kidney disease' below.)

- Anemia** – Anemia is common. In the series from the Netherlands, anemia was present in 60 percent of patients overall and positively correlated with the size and number of AMLs [27].

- Hypertension** – Hypertension is often observed. Hypertension is less common in patients who only have renal AMLs compared with patients who have renal cysts with or without AMLs. Hypertension correlates with the size and number of AMLs [27].

Malignant renal epithelioid angiomyolipomas — In contrast to the uniformly benign prognosis of classic renal AMLs, epithelioid variants may undergo malignant transformation, although this is infrequent. Malignant transformation is manifested by local recurrence and/or distal metastases. The relative risk is greater in patients with TSC, but most patients with malignant transformation have sporadic renal AMLs [30-32].

Diagnosis

Radiographic diagnosis — The diagnosis of renal AMLs is usually made by imaging studies (magnetic resonance imaging [MRI], CT, or ultrasound) and relies on the demonstration of the tumor. We generally usually use MRI for the initial screen and use ultrasound alternating with MRI to monitor growth, depending on findings. It is occasionally difficult to get good-quality MRI without motion artifact unless general anesthesia is used among patients with cognitive impairment. Ultrasound should be followed up with MRI if a lesion is detected. The international guideline recommends MRI for diagnosis and imaging every one to three years [43].

Renal angiomyolipoma on CT imaging

Image 1

The fat, if present, appears hyperechogenic on ultrasound; has a low attenuation value on CT scan (image 1); and, with MRI, appears bright on T1-weighted images, dark on T2-weighted images with fat saturation, and intermediate on T2-weighted images [6,44-47]. The early, small lesions have a characteristic radial, striated, or wedge-shaped pattern, with the base of the wedge facing the surface of the kidney. As the AMLs grow, there may be a mass effect within the renal parenchyma, or they can become exophytic (ie, grow outward).

The diagnostic accuracy often depends upon the amount of fat tissue in the tumor. A potential source of error in the interpretation of imaging studies is that small amounts of fat can be found within the borders of renal cell carcinomas (RCCs) that invade renal sinus fat (which is the major differential diagnosis to AMLs). The demonstration of fat occasionally leads to misinterpretation of an RCC as an AML. In addition, approximately 5 percent of renal AMLs contain at least components with minimal amounts of fat and are called minimal fat or fat poor. It is difficult to distinguish fat-poor AML (either classic AML [predominantly composed of smooth muscle cells] or epithelioid AML) from RCC and oncocytoma. Failure to detect fat in an AML may also be due to intratumoral hemorrhage obscuring the fat attenuation signal. (See 'Renal cell carcinoma' below.) Specific radiographic criteria have been proposed that define fat-rich, fat-poor, and fat-invisible AML based on quantitative values observed on CT and MRI [48]. A fat-invisible AML (defined by CT attenuation greater than -10 HU and an MRI tumor-to-spleen ratio of 0.71 or greater and a signal intensity index of 16.5 percent or less) requires biopsy for diagnosis [48,49]. The approach to fat-poor AML, defined by attenuation of more than -10 HU on CT images but with an MRI tumor-to-spleen ratio less than 0.71 or a signal intensity index greater than 16.5 percent, is controversial [49]. Often, combining imaging modalities can be helpful.

Radiologic features of TSC

Image 2

Several findings on CT, MRI, and CT/positron emission tomography (PET) may help to distinguish renal AMLs with no or minimal fat from RCC. These include (image 2) [50-54]:

- Adjacent fat attenuation pixels within the lesion by thin-section unenhanced CT
- Homogeneously high attenuation on unenhanced CT
- Homogeneous and prolonged enhancement pattern on dynamic contrast-enhanced CT
- Low T2 signal intensity on MRI

- Microscopic fat on in-phase and opposed-phase gradient echo MR sequences
- Homogeneous signal on diffusion-weighted MRI

Other tests have also been evaluated:

- Combining tumor to renal cortex signal intensity ratios on T1- and T2-weighted images, signal intensities on in- and opposed-phase gradient echo MRIs, and arterial-to-delayed enhancement ratio has been reported to differentiate AML without visible fat from RCC with 73 percent sensitivity, 99 percent specificity, and 96 percent accuracy [53].
- Dual-tracer 18F-fluorodeoxyglucose (FDG) and 11C-acetate PET/CT have been reported to differentiate fat-poor AMLs from RCC with 94 percent sensitivity, 98 percent specificity, and 97 percent accuracy [54]. AMLs showed negative 18F-FDG but markedly increased 11C-acetate metabolism, significantly higher than RCC.

The diagnostic approach to renal masses, including surveillance, is discussed at length elsewhere. (See "Diagnostic approach, differential diagnosis, and management of a small renal mass".)

Biopsy — When the diagnosis of renal AMLs cannot be reliably established by imaging techniques, biopsy is required to make a diagnosis. Image-guided percutaneous needle biopsy using a sheath technique should be considered as an alternative to surgical exploration [55]. The risk of bleeding following needle biopsy of a minimal-fat AML does not appear to be higher than that of a biopsy for other renal tumors, particularly when fine needles are used.

The differentiation of renal AML from RCC has become more reliable with the aid of immunocytochemical analysis. Melanocytic markers such as HMB-45 and melan A are expressed in classic and epithelioid renal AMLs but not in typical RCC, while epithelial cell-associated markers such as cytokeratin and EMA are present in RCC but not in renal AMLs [28,56-58].

An exception to this distinction occurs in rare RCCs characterized by t(6;11)(p21;q12), a chromosome translocation involving the gene for transcription factor EB [59-61]. These carcinomas consistently express HMB-45 and melan A, are often negative or only focally positive for cytokeratin, and are more common in children and young adults in the general population but would be exceedingly rare in the TSC population given the frequencies of the diseases.

Differential diagnosis — The differential diagnoses of AML include other renal masses detected by imaging, including RCC and oncocytoma, and metastatic lesions from primary tumors elsewhere. (See 'Renal cell carcinoma' below and 'Oncocytoma' below.) These entities are usually distinguished from each other by characteristic radiographic features (see 'Radiographic diagnosis' above). However, as noted above, the diagnosis may be challenging among patients with minimal-fat AMLs; such patients may require biopsy with analysis of tissue using specific immunohistochemical techniques. (See 'Biopsy' above.)

The rate of growth of the lesion may help to differentiate a slowly growing, benign AML from a more rapidly growing RCC. However, data are limited. In a study of 185 solid masses, 133 were typical AMLs, and 52 were indeterminate on CT [24]. On follow-up testing with repeat CT or MRI plus interval renal ultrasonography, only three

indeterminate masses showed rapid growth, defined as >0.5 cm per year: One was an RCC, and two were minimal-fat AMLs. (See 'Surveillance for small, stable lesions' below and "Diagnostic approach, differential diagnosis, and management of a small renal mass".)

Management

Surveillance for small, stable lesions — Because of the potential for renal AML growth throughout life, international guidelines recommend renal surveillance with MRI at the time of diagnosis and at least yearly in patients with known AMLs [43,62]. The frequency of monitoring may be reduced to every two to three years for small lesions (ie, ≤ 1 cm) if stable for at least three years (ie, no growth of preexisting lesions and no new lesions).

We avoid group I gadolinium contrast agents in these patients. (See "Nephrogenic systemic fibrosis/nephrogenic fibrosing dermopathy in advanced kidney disease".)

In patients with known renal lesions, the serum creatinine and blood pressure should be measured at least once per year.

Potential issues in women — Several clinical observations suggest that female sex hormones promote the growth of renal AMLs. These include reported increased frequency and size of renal AMLs in women, hemorrhagic complications during pregnancy, and reports of renal AML growth during pregnancy [39–42] or after treatment with exogenous hormone therapy [63].

Thus, women with known renal AMLs should be cautioned about the potential risks of pregnancy and estrogen administration, and the frequency of imaging surveillance should be increased. For women starting estrogen therapy, we suggest imaging every six months or yearly once stability has been established. If the lesions are typical fat-containing lesions, ultrasounds can be used in between the MRI scans.

For renal AMLs that are growing and large (>4 cm) or have features suggesting malignant transformation (eg, intratumoral necrosis or calcifications), a surgical consultation should be obtained. If a decision for observation is made, repeat imaging should be performed at intervals not longer than six months. Surgery should be considered if the renal AMLs continue to grow. There are no data to define a growth rate that indicates the need for surgery. The decision should take into account the clinical context, patient age, and comorbidities.

Treatment — Treatment is required in a minority of patients with renal lesions and TSC [2]. Our approach, including nephron-sparing interventions and administration of mammalian target of rapamycin (mTOR) inhibitors, depends on the clinical presentation and is discussed elsewhere. (See "Renal angiomyolipomas (AMLs): Management".)

KIDNEY CYSTS

Renal cystic disease is the second most common renal manifestation of TSC after angiomyolipomas (AMLs) and has been reported in 17 to 45 percent of TSC patients

with renal lesions and 14 to 47 percent of TSC patients overall, depending on the imaging used [2,5,6]. The three most common of renal cystic disease associated with TSC are single or multiple renal cysts, *TSC2/PKD1* contiguous gene syndrome, and glomerulocystic kidney disease [64].

Single or multiple renal cysts — In most patients with TSC, the number of renal cysts is limited, their size is small, and they cause no symptoms. The prevalence of renal cysts increases with age and may be more common in males than females (figure 1) [5,22,23]. Cysts do not require regular surveillance imaging. However, TSC patients require routine surveillance imaging for AML since most will develop AML as they age. (See 'Surveillance for small, stable lesions' above.)

***TSC2/PKD1* contiguous gene syndrome** — The *TSC2* gene and the autosomal dominant polycystic kidney disease type 1 (*PKD1*) gene lie adjacent to each other in a tail-to-tail orientation on chromosome 16 at 16p13.3. (See "Autosomal dominant polycystic kidney disease (ADPKD): Genetics of the disease and mechanisms of cyst growth", section on 'Genetics' and "Tuberous sclerosis complex: Genetics and pathogenesis", section on 'Genetics'.)

Deletions inactivating both genes are associated with polycystic kidneys, a disorder that is called the *TSC2/PKD1* contiguous gene syndrome [3,65,66]. Affected patients are usually diagnosed during the first year of life or early childhood, but rarely patients are not diagnosed until adulthood, with hypertension and renal insufficiency being the major manifestations.

These general features were illustrated in a study of 17 patients, in which the following findings were noted [3]:

- Fourteen were diagnosed in the first year of life, two at two years, and one at 10 years.
- All of the patients had enlarged cystic kidneys, with radiographic findings that resembled advanced autosomal dominant PKD. (See "Autosomal dominant polycystic kidney disease (ADPKD) in adults: Epidemiology, clinical presentation, and diagnosis".)
- Five of the patients presented with cystic kidneys before the onset of other features of TSC, initially leading to an incorrect diagnosis of early-onset autosomal dominant PKD or autosomal recessive PKD.
- Two patients developed small echogenic areas consistent with renal AMLs, which typically develop after the first year of life in these patients.
- Hypertension requiring antihypertensive drugs occurred in 12 patients.
- The glomerular filtration rate (GFR) was normal or only slightly reduced in the first 10 years of life but was markedly reduced in older patients. The three oldest patients reached end-stage kidney disease (ESKD) at ages 19, 20, and 29 years. The age of progression to ESKD is consistent with other studies and is much lower than in autosomal dominant PKD alone. (See "Autosomal dominant polycystic kidney disease (ADPKD): Treatment".)

In summary, the *TSC2/PKD1* contiguous gene syndrome should be considered in the differential diagnosis of renal cysts in children with no family history of autosomal dominant or autosomal recessive PKD, particularly in children less than two years of age. The additional finding of renal AMLs in this setting is virtually pathognomonic of TSC.

Patients with *TSC2/PKD1* contiguous gene syndrome are at risk for angiomyolipomata, and perhaps renal cell carcinoma (RCC), and require regular screening every one to three years.

Glomerulocystic kidney disease — Glomerulocystic kidney disease (ie, glomerular cysts) is a rare finding that is usually diagnosed during the neonatal period [67,68]. Seven of the eight reported cases were unilateral, and four cases had segmental lesions, with normal kidney tissue on the affected side [67]. Affected kidneys were typically enlarged and had renal cysts on imaging studies and glomerular cysts on histologic examination.

RENAL CELL CARCINOMA

Patients with TSC may be at increased risk for the development of renal cell carcinoma (RCC) [2,69-71]. It has been suggested that the increased risk may be related at least in part to the presence of hyperplasia and atypia in the cells lining renal cysts [21] (see 'Kidney cysts' above). A 'TSC-associated papillary RCC' (PRCC) has been described with a distinct morphologic, immunologic, and molecular profile. This profile includes prominent papillary architecture and uniformly deficient succinate dehydrogenase subunit B (SDHB) expression [72,73]. Other morphologic variants include a hybrid oncocytic chromophobe tumor and a granular eosinophilic macrocystic RCC. All are melanosome-associated protein (HMB-45) negative [73].

The magnitude of risk of RCC has not been well defined [2,69,70]. In a report of 167 patients with TSC cited above, four of these patients (4 percent) had RCC, and six (6 percent) had lesions on imaging in which RCC and minimal-fat renal angiomyolipomas (AMLs) could **not** be distinguished. (See 'Differential diagnosis' above.)

RCC in patients with TSC is often multifocal and bilateral. These cancers develop at an early age compared with RCCs in the general population, and there are numerous reports of RCC occurring in children [2,74-79]. The risk seems to be higher in patients with *TSC2* than *TSC1* mutations, and patients with the contiguous gene syndrome may have the greatest risk. (See '*TSC2/PKD1* contiguous gene syndrome' above.)

A diagnosis of RCC should be considered in patients with **enlarging lesions and no demonstrable fatty tissue**. If a diagnosis cannot be established by imaging, a fine-needle aspiration biopsy should be performed with both histologic examination and, to distinguish RCC from a malignant renal AML, immunohistochemical analysis. (See 'Malignant renal epithelioid angiomyolipomas' above.)

The diagnostic uncertainty in some patients is in part due to the lack of distinction in many reports between HMB-45- and melan A-positive, cytokeratin-negative epithelioid AMLs and cytokeratin-positive, HMB-45- and melan A-negative RCCs. As an example, an early study published before this distinction was fully appreciated described six patients with TSC and RCC [71]. Four of these patients had HMB-45-positive tumors, suggesting that they had a malignant AML, not RCC.

Because of the frequent bilaterality of renal lesions in TSC, ablative therapies (radiofrequency or cryotherapy) or nephron-sparing surgery should be performed whenever possible [80]. (See 'Renal angiomyolipomas (AMLs): Management'.)

LESS COMMON KIDNEY MANIFESTATIONS

Oncocytoma — Renal oncocytomas are benign tumors composed of polygonal cells with abundant, finely granular, eosinophilic cytoplasm and densely packed mitochondria. In patients with TSC, they are usually discovered during surveillance ultrasonography and evaluation for flank pain and hematuria. (See "Epidemiology, pathology, and pathogenesis of renal cell carcinoma", section on 'Oncocytomas'.) Renal oncocytomas are a more common cause of renal cell neoplasms in patients with TSC than in the general population. In a study of 36 patients with concurrent renal angiomyolipomas (AMLs) and renal cell malignancy, oncocytomas accounted for a higher proportion of renal cell malignancies in the 11 patients with TSC than in the remaining patients with sporadic renal AMLs (27 versus 8 percent) [69]. Renal oncocytomas are usually unilateral and single in the general population but may be multiple and bilateral in patients with TSC [81].

The diagnosis of renal oncocytoma should be confirmed by immunohistochemistry since epithelioid AMLs can be confused with oncocytomas.

Nephron-sparing surgery is the treatment of choice since the diagnosis cannot be definitively made with noninvasive testing. Cryoablation or radiofrequency ablation is an alternative in some centers. (See "Renal angiomyolipomas (AMLs): Management".)

Other renal lesions — A variety of other renal lesions have been infrequently described in patients with TSC. These include:

- Parapelvic or perirenal lymphatic cysts in patients with extrapulmonary lymphangiomyomatosis (LAM) [82,83].
- Medium-sized and large vessels, including the renal arteries, are rarely involved, and a few cases of renal artery stenosis and aortic coarctation have been reported [84-88].
- Other abnormalities described in TSC, such as horseshoe kidney, are probably coincidental [89-91].

CHRONIC KIDNEY DISEASE

Some patients with TSC develop chronic kidney disease (CKD) with subnephrotic proteinuria that can progress to end-stage kidney disease (ESKD) in the absence of large renal angiomyolipomas (AMLs) or extensive renal macrocystic disease [22,23,92-95]. The kidneys are typically small and echogenic on ultrasonography.

Kidney biopsy often reveals focal segmental glomerulosclerosis (FSGS), with chronic interstitial disease that is thought to be a secondary disorder induced by nephron loss [92]. The proteinuria and renal insufficiency in secondary FSGS develop slowly. This is in contrast to the course in primary FSGS, which is typically characterized by the acute or subacute onset of nephrotic syndrome. These issues are discussed in detail elsewhere. (See "Focal segmental glomerulosclerosis: Pathogenesis", section on

'Pathogenesis of secondary FSGS' and 'Focal segmental glomerulosclerosis: Clinical features and diagnosis', section on 'Classification and clinical features'.)

Some patients with TSC have a **different type of chronic interstitial disease**, in which there is a diffuse, hyperplastic appearance of the interstitial stroma, with areas of spindle, smooth muscle, and fibroblastic cells [22,84]. The pathogenesis of this disorder has not been defined. It may be mediated at least in part by the genetic deficiency in tuberin in TSC since tuberin regulates the expression and promoter activity of the cell fibrosis protein alpha-smooth muscle cell actin [96]. (See 'Tuberous sclerosis complex: Genetics and pathogenesis', section on 'Role of mTOR'.)

The typical presenting findings in this disorder include an elevated serum creatinine concentration, a benign urine sediment, normal or mildly reduced kidney size, hyperechoic kidneys on ultrasonography, and skin features of TSC that have often been overlooked by both the patient and clinicians. When performed, brain imaging reveals pathognomonic features of TSC, such as multiple calcified subependymal nodules and tubers. There is no known therapy. (See 'Tuberous sclerosis complex: Clinical features', section on 'Brain lesions' and 'Tuberous sclerosis complex: Clinical features', section on 'Dermatologic manifestations' and 'Tuberous sclerosis complex: Evaluation and diagnosis'.)

General principles of therapy — CKD of any cause can be associated with a variety of complications including volume overload, electrolyte disorders such as metabolic acidosis and hyperkalemia, hyperphosphatemia, renal osteodystrophy, and hypertension. (See 'Overview of the management of chronic kidney disease in adults'.) In addition to protecting against cardiovascular disease, the rate of progression of CKD can be reduced by lowering the blood pressure to the suggested goal and, in patients with proteinuria, by lowering protein excretion to less than 1000 mg/day via the use of an angiotensin inhibitor and, if necessary, certain other antihypertensive drugs. These issues are discussed in detail elsewhere. (See 'Antihypertensive therapy and progression of nondiabetic chronic kidney disease in adults'.)

End-stage kidney disease — Causes of ESKD include polycystic kidneys, destruction of the renal parenchyma by multiple renal AMLs, and nephrectomies to treat life-threatening hemorrhage. Patients with CKD due to secondary FSGS can also progress to ESKD (see 'Chronic kidney disease' above). Kidney disease is also an important cause of death in patients with TSC. (See 'Effect of kidney disease on patient prognosis' below.)

Management — As the treatment of the neurologic manifestations and life expectancy improve in patients with TSC, progression of CKD to ESKD will become a more important complication.

Both dialysis and kidney transplantation provide adequate means of survival in patients who develop ESKD, but the risks of renal hemorrhage and malignant transformation in TSC pose special problems. Thus, native kidney imaging should continue, and bilateral nephrectomy could be considered when a patient with TSC and ESKD enters a dialysis or kidney transplantation program [97-99].

Because of the beneficial effect of mammalian (mechanistic) target of rapamycin (mTOR) inhibitors on the cutaneous, central nervous system, and pulmonary manifestations of TSC, immunosuppressive regimens

including everolimus or sirolimus are the treatment of choice following transplantation in patients with TSC [99,100].

EFFECT OF KIDNEY DISEASE ON PATIENT PROGNOSIS

Kidney disease is the second leading cause of death in patients with TSC, after neurologic disease, and is the most common cause of death in affected adults [23,101]. Renal causes of death include end-stage kidney disease (ESKD), retroperitoneal hemorrhage, and metastatic disease. (See "Tuberous sclerosis complex: Management and prognosis", section on 'Mortality'.)

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: Chronic kidney disease in adults" and "Society guideline links: Tuberous sclerosis".)

SUMMARY AND RECOMMENDATIONS

- Kidney lesions and tuberous sclerosis complex** – Angiomyolipoma is the most common kidney lesion observed among patients with tuberous sclerosis complex (TSC) and occurs in 49 to 60 percent of TSC patients overall. Other common lesions include kidney cysts and possibly renal cell carcinoma (RCC). (See 'Angiomyolipomas' above and 'Kidney cysts' above and 'Renal cell carcinoma' above.)

- Angiomyolipoma (AML)** – The majority of patients with AML have few or no symptoms related to the kidney disease, and lesions are detected on surveillance imaging. However, some patients may present with severe hemorrhage, chronic kidney disease (CKD), anemia, or hypertension. AMLs may cause significant and occasionally life-threatening hemorrhage. (See 'Clinical presentation' above.)

- Diagnosis** – The diagnosis of kidney AMLs is usually made by magnetic resonance imaging (MRI) studies and relies on the demonstration of fat in the tumor. Lesions that are fat poor are difficult to distinguish from RCC. When the diagnosis of kidney AMLs cannot be reliably established by imaging techniques, biopsy is required to make a diagnosis. (See 'Diagnosis' above.)

- Surveillance** – We recommend kidney surveillance with MRI at the time of diagnosis and at least yearly in patients with known AMLs. Women may require more frequent imaging if they are pregnant or starting estrogen therapy. In patients with known kidney lesions, the serum creatinine should be measured at least once per year. (See 'Surveillance for small, stable lesions' above and 'Potential issues in women' above.)

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Case Report
Microscopic Kidney Disease in Tuberous Sclerosis Complex and Treatment With mTOR Inhibition

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Declining kidney function in tuberous sclerosis complex (TSC) is often attributed to large lesions, including angiomyolipomas (AMLs) and cysts, that encroach on the normal parenchyma or that require intervention and loss of parenchyma from surgical debulking or embolization. Consequently, research on inhibitors of the mammalian target of rapamycin (mTOR), a protein complex implicated in TSC pathophysiology for its role in promoting cell growth and proliferation, has largely focused on their ability to reduce AML size. Clinical guidelines distilled from this research limit mTOR inhibition as a first-line treatment to patients with large AMLs. However, chronic kidney disease (CKD) occurs in patients without large AMLs or a history of renal intervention. Alternate mechanisms postulated for CKD in TSC may suggest a role for mTOR inhibition in this population. In this report, we present 2 cases of a microscopic variant of TSC kidney disease causing declining kidney function, as well as anecdotal evidence for the use of mTOR inhibition to improve kidney function in the absence of large AMLs. We highlight the importance of annual kidney function assessment in patients with TSC and suggest a low threshold for kidney biopsy in patients with declining glomerular filtration rate without a clear etiology clinically or radiographically.

Introduction

Individuals with tuberous sclerosis complex (TSC) develop chronic kidney disease (CKD) earlier and more frequently compared to the general population.¹ Declining kidney function is commonly attributed to large lesions encroaching on the renal parenchyma, or angiomyolipoma (AML) hemorrhage and subsequent interventions (ie, embolization and nephrectomy).^{1, 2, 3} Previous studies have supported this theory in demonstrating strong associations between CKD and AML size.^{1,4,5} Consequently, research on inhibitors of the mammalian target of rapamycin (mTOR) has largely focused on their ability to reduce AML size;^{6, 7, 8, 9, 10, 11, 12, 13} and clinical guidelines limit their use as a first-line treatment to patients with AMLs larger than 3 cm in diameter.¹⁴ However, CKD is prevalent in patients without large AMLs or a history of renal intervention.⁴ Alternate mechanisms have been postulated for the progressive loss of kidney function. TSC1 or TSC2 haploinsufficiency in renal tissue without a somatic second-hit mutation may predispose to glomerular hyperfiltration and subsequent loss of glomerular filtration rate (GFR) in a similar fashion to diabetic nephropathy.² In fact, mTOR overactivity has been suggested as a mechanism of CKD in diabetic nephropathy, with mTOR inhibition preventing glomerulosclerosis and glomerular disease progression in mouse models.^{15,16} A second mechanism is the development of multiple small AMLs. In a study aimed to further delineate the relationship between CKD and AML in TSC, Vekeman et al¹ reported that a substantial proportion of patients with CKD stage 2 or higher had numerous small AML and no large AML. TSC microcystic disease has also been associated with declining kidney function.¹⁷ In a study of TSC cystogenesis, Bissler et al¹⁸ described a mechanism involving mTOR overactivity with rapamycin administration resulting in prolonged survival of mouse models. These potential mechanisms for CKD in TSC may suggest a role for oral mTOR inhibitors everolimus and sirolimus in treating TSC patients with declining GFR in the absence of AML larger than 3 cm in diameter. Further research is needed to characterize the pathophysiology of CKD in TSC patients without large AML and the therapeutic role for mTOR inhibition. To this end, we present 2 cases of a microscopic variant of TSC kidney disease in patients with declining GFR in

Section snippets

Case 1

Patient 1 is a 26-year-old female patient diagnosed with TSC in early childhood causing complex partial epilepsy and typical skin manifestations. Genetic testing revealed 1 likely pathogenic variant in TSC1 denoted c.965dupT (p.Met322Ilefs*19) not reported previously or carried by either parent. There were no deletions in TSC2, excluding the possibility of a contiguous gene syndrome (CGS) with *PKD1*. By adulthood, she had outgrown her seizures, and TSC renal manifestations became the primary

Discussion

CKD in TSC typically occurs in the setting of large renal lesions that encroach on the normal renal parenchyma or that require intervention and loss of parenchyma from surgical debulking or embolization.^{1, 2, 3} In this report, we have presented 2 cases of a microscopic variant of TSC kidney disease causing declining kidney function in the absence of large lesions. In the first patient, kidney function improved from stage G4 to stage G3b disease and remained stable for 5 years following

Article Information

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The authors declare that they have obtained written consent from each patient reported in this article for publication of the information about him/her that appears within this Case Report and any associated supplementary material.

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Fever in infants and children: Pathophysiology and management

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INTRODUCTION

Fever is an abnormal elevation of body temperature that occurs as part of a specific biologic response that is mediated and controlled by the central nervous system.

The pathophysiology and treatment of fever in infants and children will be reviewed here. Other causes of elevated body temperature in children and the evaluation and management of fever in specific populations of infants and children are discussed separately:

- (See "Heat stroke in children" and "Heat illness (other than heat stroke) in children".)
- (See "The febrile infant (29 to 90 days of age): Outpatient evaluation" and "Fever without a source in children 3 to 36 months of age: Evaluation and management".)
- (See "Evaluation and management of fever in children and adults with sickle cell disease".)
- (See "Fever of unknown origin in children: Etiology" and "Fever of unknown origin in children: Evaluation".)
- (See "Evaluation of children with non-chemotherapy-induced neutropenia and fever" and "Management of children with non-chemotherapy-induced neutropenia and fever".)
- (See "Fever in children with chemotherapy-induced neutropenia".)

TEMPERATURE MEASUREMENT

Site and method of measurement — The most common sites of temperature measurement in clinical practice are the rectum, mouth, and axilla; in addition, parents and caregivers may measure temperature at the tympanic membrane or forehead (temporal artery). Each of these sites has its own range of normal values [1].

- Rectal thermometry** – Rectal thermometry is generally considered the reference standard for measurement of core body temperature [2], but there is a lag between changes in core body temperature and temperature in the rectal vault [3]. Rectal thermometry is usually performed in infants and young children if the result has clinical implications. The majority of studies establishing the risk of serious infections in febrile infants and young children have relied on rectal temperatures. Rectal thermometry is contraindicated in patients with neutropenia.

- Oral thermometry** – Oral thermometry generally is preferred in children who are old enough to cooperate. Oral temperature is typically 0.6°C (1.0°F) lower than rectal temperature because of mouth breathing, which is particularly important in patients with tachypnea. Oral temperatures also may be affected by recent ingestion of hot or cold liquids [1,4].

Opinions differ about the best site of temperature measurement for young children who cannot cooperate with oral thermometry. The Bright Futures Guidelines for Health Supervision suggest rectal thermometry for children younger than four years of age [5]. In contrast, the National Institute for Health and Care Excellence recommends electronic axillary thermometry for children younger than four weeks, and axillary (electronic or chemical dot) or infrared tympanic membrane (TM) thermometry for children four weeks to five years of age because these methods are quicker, easier to use, and better accepted by children and their caregivers [6].

- Axillary thermometry** – Axillary temperature is consistently lower than rectal temperature, but the absolute difference varies too widely for a standard conversion [7]. Axillary temperatures may be measured in neutropenic patients who are unable to use an oral thermometer.

- Contact and noncontact infrared thermometry** – Infrared TM thermometers measure the amount of heat produced by the TM. Temperature readings are close to core temperature, although the infrared TM reflective devices commonly used in homes, hospitals, and offices are less accurate than TM thermistors used in research and by anesthesiologists [3,8-12]. Individual studies comparing TM and rectal temperatures in children have had contradictory results. Although newer-generation infrared TM thermometers appear to have improved accuracy compared with older models (using rectal thermometry as the standard) [13], results should be verified in situations where detection of fever has clinical implications (eg, laboratory evaluation of the febrile neonate or young infant) [2]. Infrared contact and noncontact forehead thermometers measure the amount of heat produced by the temporal arteries. The accuracy of such measurements may be affected by sweating or vascular changes [1]. As with tympanic temperature measurement, studies comparing temporal artery and rectal temperatures have contradictory results, and temporal artery temperatures should not be used to make clinical decisions [2,3,14-26]. Readings may be greater or lower than rectal temperature.

•**Smart phones** – Apps for smart phones that permit tracking of fever are available. They require an external sensor, with accuracy commensurate with that of the sensor. In the absence of adequate study, they cannot be recommended for use.

Converting between Fahrenheit and Celsius — Fahrenheit and Celsius temperature equivalents are provided in the table (table 1) or can be calculated (calculator 1).

- To convert a temperature measured in Fahrenheit to Celsius:
• $(\text{Temperature in } ^\circ\text{F} - 32) \times (5/9) = \text{Temperature in } ^\circ\text{C}$
- To convert a temperature measured in Celsius to Fahrenheit:
• $[(9/5) \times \text{Temperature in } ^\circ\text{C}] + 32 = \text{Temperature in } ^\circ\text{F}$

TEMPERATURE HOMEOSTASIS

Body temperature is controlled by the thermoregulatory center of the hypothalamus. The thermoregulatory center balances heat production, derived primarily from metabolic activity in muscle and the liver, with heat dissipation from the skin and lungs. The thermoregulatory center is able to maintain a fairly steady body temperature in normal temperature environments. However, at environmental temperatures higher than approximately 35°C (95°F), the body's ability to dissipate heat is overwhelmed, and core temperature rises. (See "Heat stroke in children", section on 'Pathophysiology'.)

NORMAL BODY TEMPERATURE

The mean normal temperature is generally considered to be 37°C (98.6°F) [27]. This value usually is attributed to studies dating to the 19th century. In a more recent study of young adults, the upper limit of normal body temperature (measured orally) was 37.2°C (98.9°F) in the morning and 37.7°C (99.9°F) overall [28]. Normal body temperature varies with age, time of the day, level of activity, and phase of the menstrual cycle, among other factors [1,4].

Infants and young children generally have higher temperatures than older children and adults. This relates to the greater surface-area-to-body-weight ratio and the higher metabolic rate of infants and small children. In the newborn period (age 0 to 28 days), the mean normal temperature (measured rectally) is 37.5°C, with an upper limit of normal (ie, two standard deviations above the mean) of 38°C (100.4°F) [29].

Normal temperature varies daily, with a morning nadir and late afternoon/early evening peak. The mean amplitude of variation is 0.5°C (0.9°F) [28]. During a febrile illness, daily low and high temperature readings are maintained, but at higher-than-normal levels. Daily variation can be as high as 1°C (1.8°F) in some individuals recovering from a febrile illness.

ELEVATED BODY TEMPERATURE

Elevated body temperature may result from fever (increased body temperature with elevated hypothalamic set-point) or hyperthermia (increased body temperature with

normal hypothalamic set-point) (figure 1). It is important to differentiate between these conditions because they have different clinical implications and management strategies. (See 'Management of fever' below and 'Heat stroke in children', section on 'Hospital management'.)

Fever — Fever is an abnormal elevation of body temperature that occurs as part of a specific biologic response that is mediated and controlled by the central nervous system. (See 'Pathogenesis' below.)

The temperature elevation that is considered "abnormal" depends upon the age of the child and the site of measurement. The temperature elevation that may prompt clinical investigation for infection depends upon the age of the child and the clinical circumstances (eg, immune deficiency, sickle cell disease, ill-appearance, etc); in most scenarios, the height of the fever is less important than other signs of serious illness (eg, irritability, meningismus) [30-33].

- In the otherwise healthy infant younger than three months of age, fever of concern generally is defined by rectal temperature $\geq 38.0^{\circ}\text{C}$ (100.4°F). (See 'The febrile infant (younger than 90 days of age): Definition of fever', section on 'Definition of fever'.)
- In children 3 to 36 months, fever generally is defined by rectal temperatures ranging from ≥ 38.0 to 39.0°C (100.4 to 102.2°F) and fever of concern by rectal temperatures $\geq 39.0^{\circ}\text{C}$ (102.2°F) if there is no focus of infection on examination. (See 'Fever without a source in children 3 to 36 months of age: Evaluation and management', section on 'Fever of concern'.)
- In older children and adults, fever may be defined by oral temperatures ranging from ≥ 37.8 to 39.4°C (100.0 to 103.0°F) and fever of concern by oral temperatures $\geq 39.5^{\circ}\text{C}$ (103.1°F).
- The temperature thresholds of concern for children with underlying conditions (eg, sickle cell disease, neutropenia) are discussed separately:
 - Sickle cell disease (see "Evaluation and management of fever in children and adults with sickle cell disease")
 - Neutropenia (see "Fever in children with chemotherapy-induced neutropenia" and "Management of children with non-chemotherapy-induced neutropenia and fever", section on 'Definitions')

Pathogenesis — Fever is the result of a highly coordinated series of events that begins peripherally with the synthesis and release of interleukin (IL)-1, IL-6, tumor necrosis factor, interferon-alpha, and other endogenous pyrogenic cytokines by phagocytic cells in the blood or tissues (figure 2) [34]. These cytokines enter the blood and are carried to the anterior hypothalamus, where they induce an abrupt increase in the synthesis of prostaglandins, especially prostaglandin E2 (PGE2). The induction of PGE2 in the brain raises the hypothalamic set-point for body temperature (figure 1).

After the set-point is raised, the thermoregulatory center recognizes current body temperature to be too low and initiates a series of events to raise body temperature to the new set-point. This involves augmentation of heat production by increased metabolic rate and increased muscle tone and activity, and decreased heat loss through diminished perfusion of the skin. Body temperature rises until a new equilibrium is achieved at the elevated set-point. The upper limit of temperature due to fever appears

to be 42°C (107.6°F), but it is unusual for temperature to exceed 41°C (106°F) without some element of concomitant hyperthermia [1,35,36].

In addition to causing fever, pyrogenic cytokines increase the synthesis of acute-phase proteins by the liver, decrease serum iron and zinc levels, provoke leukocytosis, and accelerate skeletal muscle proteolysis. IL-1 also induces slow-wave sleep, perhaps explaining the somnolence frequently associated with febrile illnesses. The increase in peripheral PGE2 may account for the myalgias and arthralgias that often accompany fever. Increased heart rate is a normal physiologic response to fever.

Benefits and harms — Whether fever is beneficial or harmful is disputed [36]. Fever is an integral part of the inflammatory response and, as such, may have a role in fighting infection. However, defense mechanisms can go awry. Even if fever does have a role in defending the host against infection, it may still be that, in some circumstances, fever does more harm than good [37,38].

- Potential benefits** – Potential benefits of fever include retardation of the growth and reproduction of some bacteria and viruses (perhaps related to decreased serum iron) and enhanced immunologic function at moderately elevated temperatures (although some of the benefits are reversed at temperatures approaching 40°C [104°F]) [36,39-45]. Some animal studies have demonstrated enhanced survival with fever [46,47]. However, as with immune function, the benefits may be diminished or even reversed as temperature increases [47,48]. Whether these findings apply to humans is not known.

- Potential harms** – Fever can make patients uncomfortable. It is associated with increased metabolic rate, oxygen consumption, carbon dioxide production, and demands on the cardiovascular and pulmonary systems. For the normal child, these stresses are of little or no consequence. However, for the child in shock or for the child with a pulmonary or cardiac abnormality, the increased demands can be detrimental and may offset any immunologic benefit from the fever.

In experimental studies, fever has been associated with impaired immunologic responses (eg, phagocytosis of staphylococci and lymphocyte transformation in response to mitogens) and cerebral injury (including edema and hemorrhage) [49-51]. Whether these findings apply to humans is not known.

There is no evidence to suggest that fever ≥40°C (104°F) is associated with increased risk of adverse outcome (eg, brain damage), although this belief is held by many caregivers and clinicians [39,52,53].

Hyperthermia — Hyperthermia is an abnormal elevation of body temperature that occurs without a change in the thermoregulatory set point in the hypothalamus (figure 1). This failure of normal homeostasis results in heat production that exceeds the body's capacity for dissipation [39]. Body temperature in patients with hyperthermia does not respond to antipyretic agents.

Characteristic clinical features of hyperthermia include a history of environmental heat exposure or use of drugs that interfere with normal thermoregulation (eg, anticholinergics); hot, dry skin; and central nervous system dysfunction (eg, delirium, convulsions, coma). Hyperthermia can be rapidly fatal; adverse physiologic effects begin to occur at temperatures >41°C (105.8°F). (See "Heat stroke in children", section

on 'Clinical features' and "Heat illness (other than heat stroke) in children", section on 'Clinical manifestations and treatment'.)

EVALUATION OF FEVER

Fever is a sign of underlying disease, the cause of which should be evaluated, particularly if the child is ill-appearing or the fever persists. The response of fever to an antipyretic agent does not help to distinguish bacterial from viral infection [54-56]. When determining whether the child needs to be seen by a health care provider, caregivers' concern about their child's appearance is more important than the response of fever to antipyretic agent(s). In most cases, the febrile child has additional symptoms and signs of an acute infection, which can be managed as indicated. However, in some children, particularly children with underlying disease, fever may be a sign of a more serious or even life-threatening process.

The evaluation of fever in specific populations of children is discussed separately:

- (See "The febrile infant (29 to 90 days of age): Outpatient evaluation" and "Fever without a source in children 3 to 36 months of age: Evaluation and management".)
- (See "Fever of unknown origin in children: Etiology" and "Fever of unknown origin in children: Evaluation".)
- (See "Evaluation and management of fever in children and adults with sickle cell disease".)
- (See "Evaluation of children with non-chemotherapy-induced neutropenia and fever" and "Evaluation of children with non-chemotherapy-induced neutropenia and fever", section on 'Evaluation'.)
- (See "Fever in children with chemotherapy-induced neutropenia".)

MANAGEMENT OF FEVER

Fever is an important clinical sign. The first step in the management of fever is to determine its cause (see 'Evaluation of fever' above). Once the cause is known, the main reason to treat fever is to improve the child's comfort [39,57].

Anticipatory guidance — Patients, parents, and other caregivers frequently make the decision to treat fever without consulting a health care provider. Many patients and caregivers believe that fever is harmful and that temperature elevation requires treatment regardless of its cause or effects [52,58-60]. Education of patients, parents, and caregivers is required to counter these beliefs [4,36,39]. Such education should be provided at health supervision visits and reinforced during acute visits for acute febrile illnesses. A systematic review of eight studies evaluating anticipatory guidance for fever and common infections concluded that educational interventions provided before the illness episodes had the potential to improve medication management and parental health care-seeking behavior when the child became ill [61].

Important components of the anticipatory guidance for fever include [4,6,36,39,54-56]:

- Fever is not an illness but a physiologic response.

- In otherwise healthy children, most fevers are self-limited and benign, provided that the cause is known and fluid loss is replaced; fever does not cause brain damage. If there are signs of serious illness, a health care provider should be consulted.
 - There is no evidence that fever makes the illness worse.
 - Initial measures to reduce the child's temperature include provision of extra fluids and reduced activity.
 - Fever may merit treatment with an antipyretic agent if the child is uncomfortable (as indicated by decreased activity level, decreased fluid intake, etc).
 - Decreased temperature after receiving an antipyretic agent does not help to determine whether the child has a bacterial or viral infection.
 - Children who are receiving treatment for fever do not need to be awakened to receive the antipyretic agent.
 - Children who are receiving antipyretic medications should not be given combination cough and cold preparations, which often contain antipyretic medications; giving both medications may lead to inadvertent overdose.
 - Antipyretic medications should be dosed according to weight, rather than age.
- When suggesting the use of antipyretic medications, the risk of under- or overdosing antipyretics can be minimized if the clinician provides written dosing instructions and a measuring device, such as a properly marked syringe (for liquid formulations); the dosing directions and measuring devices that are included with over-the-counter medications are variable and inconsistent [62]. The instructions should include which formulation (or which concentration of a liquid formulation); how to measure the appropriate volume (for liquid formulation); how often to administer; how to monitor the response; when to discontinue; and when to contact the health care provider.
- Instructions for safe storage of antipyretic medications.

Antipyretic agents — Antipyretic agents treat fever by restoring the thermoregulatory set-point to normal. The most commonly used antipyretic agents in children and adolescents are acetaminophen and ibuprofen. Aspirin should not be used because of its association with Reye syndrome [39].

Indications — Routine treatment of fever in otherwise normal children is not warranted [1,6]. Decisions regarding the treatment of fever in children should be made on a case-by-case basis depending upon the clinical circumstances (eg, underlying disease, level of discomfort, desire to monitor fever curve).

There is no evidence that reducing fever reduces the morbidity or mortality from a febrile illness (with the possible exception of children with underlying conditions that limit the ability to tolerate increased metabolic demands). The role of antipyretic therapy in recurrence of febrile seizures is discussed separately. (See "Treatment and prognosis of febrile seizures", section on 'Antipyretics'.)

Potential benefits of treating fever with antipyretics include improvement of discomfort and decrease in insensible water loss, which may decrease the risk of dehydration [39]. Antipyretic agents also have analgesic effects, which may enhance their overall effect. Potential downsides of treating fever include delayed identification of an underlying illness and drug toxicity; it is uncertain whether treating fever increases the risk for or complications of certain types of infections. (See 'Benefits and harms' above.)

Indications for the short-term treatment of fever may include [1,36]:

- Shock
- Underlying neurologic or cardiopulmonary disease, or other condition with increased metabolic rate (eg, burn, postoperative state)
- Alteration in fluid and electrolyte balance
- High fever (ie, $\geq 40^{\circ}\text{C}$ [104°F])
- Discomfort
- Major head trauma
- Postcardiac arrest

Children with temperature elevation and the possibility of hyperthermia also require treatment, but the treatment of hyperthermia differs from that of fever. Antipyretic medications are ineffective in children with heat stroke and may exacerbate concomitant liver injury or coagulopathy. (See "Heat stroke in children", section on 'Hospital management' and "Heat illness (other than heat stroke) in children", section on 'Clinical manifestations and treatment'.)

Suggested approach — The choice of antipyretic agent for children with underlying medical conditions may be influenced by the underlying medical conditions (eg, avoidance of acetaminophen in children with liver failure) or desire to avoid drug interactions with chronic medications (eg, selective serotonin reuptake inhibitors may enhance the antiplatelet effect of ibuprofen).

When antipyretic therapy is indicated for children without underlying medical conditions, or with underlying medical conditions that do not influence the choice of antipyretic, we suggest beginning treatment with oral acetaminophen. Oral ibuprofen is an alternative to acetaminophen, particularly if anti-inflammatory effect is desired in addition to antipyresis. Patient/caregiver preference is a major factor in the choice of antipyretic because patients/caregivers frequently make the decision to treat fever without consulting a health care provider. In randomized trials, acetaminophen and ibuprofen are more effective than placebo in reducing temperature; ibuprofen is slightly more effective and longer-lasting than acetaminophen [63,64]. However, we prefer acetaminophen because of its long track record of safety with therapeutic dosing [1]. (See 'Acetaminophen' below and 'Ibuprofen' below.)

We do not suggest combining or alternating acetaminophen with ibuprofen because of the potential for dosing confusion, increased toxicity, and contribution to fever phobia [39,57,65,66]. Although combining or alternating acetaminophen and ibuprofen may be more effective than either agent alone in reducing fever, it is not clear that this temperature reduction is clinically significant [67,68]. In addition, there is little information about the effects on the child's discomfort or the safety of combining or alternating antipyretic therapy, and there are theoretic concerns of liver or kidney injury, particularly for children with volume depletion [67,69-71]. (See 'Combining or alternating therapy' below.)

If the temperature remains elevated and the child's discomfort is not improved three to four hours after administration of acetaminophen or ibuprofen, it is reasonable to **switch** from acetaminophen to ibuprofen or ibuprofen to acetaminophen [6]. (See 'Treatment response' below.)

Antipyretic regimens

Acetaminophen — For most children with fever who are treated with an antipyretic agent, we suggest oral acetaminophen because of its long track record of safety at therapeutic doses [1]. Although oral acetaminophen is preferred to rectal acetaminophen because the drug concentration is more predictable, short-term (ie, <48 hours) rectal administration is an option for children who cannot take acetaminophen orally [72].

Acetaminophen generally is not recommended for infants younger than three months of age without prior consultation with a health care provider because fever may be the only sign of serious infection in such infants. (See "The febrile infant (29 to 90 days of age): Outpatient evaluation", section on 'Invasive bacterial infection' and "The febrile neonate (28 days of age or younger): Outpatient evaluation", section on 'Invasive bacterial infection'.)

The dose of acetaminophen is 10 to 15 mg/kg per dose (maximum dose 1 g) orally every four to six hours (with no more than five doses in a 24-hour period) with a maximum daily dose of 75 mg/kg per day up to 4 g/day (some formulations suggest a lower maximum daily dose). We do not recommend a "loading dose" (eg, an initial dose of 30 mg/kg) of acetaminophen for routine clinical care because it may increase the risk of dosing confusion [39].

Approximately 80 percent of febrile children who are treated with acetaminophen have a reduction in temperature of 1 to 2°C (1.8 to 3.6°F) [39,73]. Acetaminophen begins to work in 30 to 60 minutes and has its peak effect in three to four hours. The duration of action is four to six hours.

When administered at appropriate doses, acetaminophen is remarkably free of side effects [74,75]. In August 2013, the US Food and Drug Administration (FDA) issued a safety communication about serious and potentially fatal acetaminophen-associated skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, and acute generalized exanthematous pustulosis that can occur with the first exposure to acetaminophen or at any time during use [76]. These reactions are rare (the FDA review found a total of only 107 cases between 1969 and 2012) and can occur with other antipyretic agents. Children who develop skin lesions while using acetaminophen should discontinue acetaminophen and seek prompt medical attention. (See "Stevens-Johnson syndrome and toxic epidermal necrolysis: Pathogenesis, clinical manifestations, and diagnosis" and "Acute generalized exanthematous pustulosis (AGEP)".)

An association between acetaminophen and asthma has been described, but causality has not been demonstrated. (See "Risk factors for asthma", section on 'Acetaminophen'.)

Overdose of acetaminophen may be lethal. Overdose may occur if acetaminophen is administered simultaneously with combination cough and cold remedies that contain acetaminophen, with unsupervised ingestion, and with unclear instructions for administration [39,77]. (See "Clinical manifestations and diagnosis of acetaminophen (paracetamol) poisoning in children and adolescents", section on 'Epidemiology'.)

Ibuprofen — For children ≥6 months of age in whom antipyretic and anti-inflammatory activity are desired (eg, in children with juvenile arthritis) and who are well hydrated, we suggest oral ibuprofen as the initial antipyretic agent [1].

The dose of ibuprofen is 10 mg/kg per dose (maximum dose 600 mg) orally every six hours with a maximum daily dose of 40 mg/kg up to 2.4 g/day [39]. Ibuprofen begins to work in <60 minutes and has its peak effect (decline in temperature of 1 to 2°C [1.8 to 3.6°F]) in three to four hours. The duration of action is six to eight hours [39,73].

Ibuprofen generally is not recommended for infants <3 months of age without prior consultation with a health care provider because fever may be the only sign of serious infection in such infants. (See "The febrile infant (29 to 90 days of age): Outpatient evaluation", section on 'Invasive bacterial infection' and "The febrile neonate (28 days of age or younger): Outpatient evaluation", section on 'Invasive bacterial infection'.)

Recommendations for ibuprofen in infants between three and six months of age vary geographically [78]. In the United States, ibuprofen suspension is approved for antipyresis in infants ≥6 months of age. In other countries, it may be approved for infants ≥3 months of age who weigh ≥5 kg. Infants <6 months of age are potentially at increased risk for kidney toxicity because they have limited kidney function relative to older infants and children [39]. Few studies have directly evaluated the risk of kidney toxicity when ibuprofen is used to treat fever in infants <6 months of age, and the magnitude of risk is uncertain [63,78-82].

Adverse effects of ibuprofen may include gastritis and gastrointestinal bleeding [83].

When administered at appropriate doses and taken with food, ibuprofen usually is safe [75,84]. However, acute kidney injury has been reported following appropriate doses of ibuprofen [85]. Anecdotal reports have linked nonsteroidal anti-inflammatory drugs with the development or more rapid progression of necrotizing fasciitis due to group A streptococci in children with varicella [86,87]. However, a review of the literature, including five prospective studies, did not demonstrate a correlation [88].

Overdose may occur if ibuprofen is administered simultaneously with combination cough and cold remedies that contain ibuprofen, with unsupervised ingestion, and unclear instruction for administration [39]. Overdose of ibuprofen appears more easily managed than overdose of acetaminophen [89]. (See "Nonsteroidal antiinflammatory drug (NSAID) poisoning", section on 'Pediatrics'.)

Combining or alternating therapy — We do not suggest combining or alternating therapy with acetaminophen and ibuprofen to treat fever in children. Although combining or alternating acetaminophen and ibuprofen may be more effective than either agent alone in reducing fever, it is not clear that this reduction is clinically significant [67,68]. In addition, there is little information about the effects on the child's discomfort or the safety of combining or alternating antipyretic therapy, and there are theoretic concerns of liver or kidney injury, particularly for children with volume depletion [67,69-71].

A 2013 systematic review included six randomized trials (915 patients) evaluating combination or alternating versus single agent antipyretic therapy in children [67]. The individual trials used different thresholds for fever, sites of temperature measurement (eg, rectal, axillary), dosing regimens, and periods of observation for outcome assessment [68,80,90-94].

- In pooled analysis, combination therapy resulted in decreased mean temperature one hour after treatment (mean difference -0.27°C [-0.48°F], 95% CI -0.45 to -0.08°C [-0.81°F to -0.14°F]; two trials, 163 patients) and four hours after treatment (mean difference -0.70°C [-1.26°F], 95% CI -1.05 to -0.35°C [-1.89°F to -0.63°F]; two trials, 173 patients) although the mean temperature in the single-agent group

one and four hours after treatment was $<38^{\circ}\text{C}$ (100.4°F) [67]. Fewer children receiving combination therapy remained or became febrile four hours after treatment (2 versus 23 percent; risk ratio [RR] 0.08, 95% CI, 0.02-0.42; two trials, 196 patients).

In pooled analysis, alternating therapy was associated with decreased mean temperature one hour after the second agent (mean difference -0.60°C [-1.08°F], 95% CI -0.94 to -0.26°C [-1.69°F to -0.47°F]; two trials, 78 patients) although the mean temperature in the single-agent group was $\leq 38^{\circ}\text{C}$ (100.4°F) [67]. Fewer children receiving alternating therapy remained or became febrile three hours after the second agent (11 versus 45 percent; RR 0.25, 95% CI 0.11-0.55; two trials, 109 patients).

One trial compared combination with alternating therapy and found no difference in mean temperature reduction or proportion of children who remained or became febrile [94].

- Among the trials that assessed measures other than temperature, one found no difference in child discomfort between combination and single-agent therapy [93]; one found that caregivers perceived no difference in efficacy despite greater temperature reduction with alternating therapy [68]; and one found that children who received alternating antipyretic therapy had lower scores on a pain checklist than those who received single agent therapy, although it was not clear that the assigned antipyretic regimens were followed appropriately (children assigned to the alternating group received a lower mean number of doses of antipyretic than those assigned to single-agent therapy), making the results difficult to interpret [91].

- No serious adverse events were observed in the trials that reported serious adverse events of combining or alternating therapy [68,91-93]. In one trial, mild, transient elevation of liver enzymes and mildly abnormal kidney function occurred in 1.7 and 3 percent of participants, respectively, but did not differ between groups [91].

The American Academy of Pediatrics (AAP) clinical report on fever and antipyretic use in children suggests that combined treatment with acetaminophen and ibuprofen may increase the possibility of inaccurate dosing and may contribute to "fever phobia" [39]. Similarly, the Italian Pediatric Society guidelines for the management of fever in children recommend against the combined use of acetaminophen and ibuprofen [57]. The National Institute for Health and Care Excellence advises against the simultaneous use of acetaminophen and ibuprofen and suggests that alternating these agents be considered only if the child's distress or discomfort persists or recurs before the next dose is due [6]. If the decision is made to use combined or alternating therapy, dosing instructions and intervals must be thoroughly explained. (See 'Anticipatory guidance' above.)

Duration — The duration of administration of antipyretic therapy depends upon the child's response; the end-point is the child's comfort [39]. Prolonged use of antipyretic agents generally is not necessary because most febrile illnesses in children are self-limited viral infections. Re-evaluation for secondary bacterial infection may be warranted in children whose fever and discomfort persist for more than two to three days.

Treatment response — Treatment with antipyretic agents should make the febrile child more comfortable. It is more important for caregivers to monitor the child's general appearance (for signs of serious illness such as lethargy, stiff neck, altered mental status, petechial or purpuric rash, etc), activity level, and fluid intake than to monitor the temperature curve and to seek medical care if they are concerned about their child's appearance. With either acetaminophen or ibuprofen, a response should be seen within 60 minutes; the response peaks in three to four hours [39]. If the temperature remains elevated and the child's discomfort is not improved three to four hours after administration of acetaminophen or ibuprofen, some experts would suggest switching from acetaminophen to ibuprofen or ibuprofen to acetaminophen [6]. There are no published studies to evaluate the safety or efficacy of this practice; however, in theory, some fevers may respond better to one antipyretic agent than another.

Persistence of a febrile illness beyond four or five days, a marked increase in the height of the maximum fever during the course of the illness, or the development of new localizing symptoms should raise concerns about alternative diagnoses or bacterial superinfection, which should be evaluated by a health care provider (or re-evaluated by a health care provider if the child was seen at the onset of illness) [39].

Use in young infants — The AAP clinical report on fever and antipyretic use in children suggests that acetaminophen not be administered to infants younger than three months and that ibuprofen not be administered to children younger than six months without evaluation by a clinician [39]. Fever may be the only sign of serious infection in a young infant, and such infections should be excluded before symptomatic treatment of fever is initiated. (See "The febrile infant (29 to 90 days of age): Outpatient evaluation", section on 'Invasive bacterial infection' and "The febrile neonate (28 days of age or younger): Outpatient evaluation", section on 'Invasive bacterial infection'.)

Decisions regarding the use of acetaminophen in infants younger than three months after serious infection has been excluded should be made on a case-by-case basis. The safety of acetaminophen in young infants can be extrapolated from its use as an analgesic in this population (see "Management and prevention of pain in neonates", section on 'Acetaminophen'). However, there is little information about its efficacy as an antipyretic.

External cooling — External cooling is the treatment of choice for heat stroke and other forms of heat illness in which rapid cooling is necessary to prevent end-organ damage. (See "Heat stroke in children", section on 'Rapid cooling' and "Heat illness (other than heat stroke) in children", section on 'Clinical manifestations and treatment'.) We do not routinely suggest external cooling for temperature reduction in previously well infants and children with a febrile illness. In randomized trials comparing the combination of tepid sponging and antipyretic therapy to antipyretic therapy alone, the added benefit of tepid sponging in temperature reduction was short-lived, and sponging was associated with increased discomfort [95-97].

External cooling may be used as an adjunct to antipyretic therapy for children in whom more rapid and greater reduction of body temperature is necessary than can be achieved with antipyretic agents alone. In such cases, antipyretic agents should be administered at least 30 minutes before external cooling [4]. Antipyretic agents are necessary to reset the thermoregulatory set-point, without which external cooling will result in an increase in heat production [1].

Possible indications for concomitant antipyretic administration and mechanical cooling in children include:

- Uncertainty about the cause of elevated temperature (heat illness versus fever) (see 'Hyperthermia' above)
- Fever combined with a component of heat illness (eg, from over-wrapping, hypovolemia, or drugs such as atropine)
- Underlying neurologic disorder, in which the child may have abnormal temperature control and poor response to antipyretic agents

When mechanical cooling is necessary to treat fever, we suggest sponging with comfortably warm or tepid water (generally around 30°C [85°F]). Sponging is more effective than immersion because evaporation from the skin augments heat loss. Although temperature reduction may be faster with cold water, sponging with cold water is also more uncomfortable. Alcohol should not be used because its fumes are absorbed across the alveolar membrane and possibly across the skin, resulting in central nervous system toxicity [98].

Cooling blankets can be useful in hospitalized children who are critically ill or who have problems with temperature control (eg, children with acute head injury).

Alternative therapies — Practitioners of complementary and alternative therapy may suggest a number of remedies for fever in infants and children (eg, calcium lactate). These remedies have not been studied in clinical trials, and there is little to no information about their efficacy or safety. We do not recommend their use.

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: Fever in children".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or email these topics to your patients. (You can also locate patient education

articles on a variety of subjects by searching on "patient education" and the keyword[s] of interest.)

- Basics topic (see "Patient education: Giving your child over-the-counter medicines (The Basics)")
- Beyond the Basics topic (see "Patient education: Fever in children (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- Terminology** – Fever is an abnormal increase in body temperature that results from elevation of the hypothalamic set-point (figure 2). The magnitude of temperature increase that prompts evaluation depends upon the age of the child and the clinical circumstances. (See 'Fever' above.)
- Evaluation of fever** – The cause of fever should be evaluated, particularly in infants younger than three months of age and infants and children with underlying medical conditions that increase the risk of serious infection (eg, sickle cell disease, neutropenia). (See 'Evaluation of fever' above.)
- Indications for treatment** – Decisions regarding the treatment of fever in children should be made on a case-by-case basis. Indications for the treatment of fever may include shock, underlying medical conditions that would be exacerbated by increased metabolic demand, fluid or electrolyte imbalance, temperature $\geq 40^{\circ}\text{C}$ (104°F), and discomfort. (See 'Indications' above.)
- Suggested approach** – The choice of antipyretic agent for children with underlying medical conditions may be influenced by the underlying medical condition and chronic medications. (See 'Suggested approach' above.)
 - When the decision is made to use an antipyretic agent in a child without an underlying medical condition, or with an underlying medical condition that does not influence the choice of antipyretic, we suggest beginning treatment with acetaminophen (**Grade 2B**). The dose is 10 to 15 mg/kg per dose (maximum dose 1 g) orally every four to six hours (with no more than five doses in a 24-hour period; maximum daily dose: 75 mg/kg per day up to 4 g/day). (See 'Acetaminophen' above.)
 - Ibuprofen is an alternative to acetaminophen, particularly if anti-inflammatory effect is desired. The dose of ibuprofen is 10 mg/kg per dose (maximum dose 600 mg) orally every six hours (maximum daily dose: 40 mg/kg up to 2.4 g/day). (See 'Ibuprofen' above.)
 - We suggest not combining or alternating acetaminophen with ibuprofen (**Grade 2B**). (See 'Combining or alternating therapy' above.)
 - If the temperature remains elevated and the child's discomfort is not improved three to four hours after administration of acetaminophen or ibuprofen, some experts suggest switching from acetaminophen to ibuprofen or ibuprofen to acetaminophen. (See 'Treatment response' above.)
 - Prolonged use of antipyretic agents generally is not necessary. Persistence of fever beyond four or five days, a marked increase in the height of the fever

during the course of illness, or the development of new localizing symptoms should raise concerns about alternative diagnoses or bacterial superinfection, which should be evaluated. (See 'Duration' above.)

•For previously well infants and children with a febrile illness, we suggest not using external cooling for temperature reduction (**Grade 2A**). (See 'External cooling' above.)

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A possible rare cause of renal failure in streptococcal infection

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Abstract

To the best of our knowledge, this is the first biopsy-proven case of streptococcal infection-associated acute interstitial nephritis (AIN) with existence of streptococcal pyrogenic exotoxin B (SPE B) by a controlled immunohistochemical method. Both the intact tubular epithelial cells and oedematous interstitium had strong positive signals, whereas only interstitial inflammation was dominant without tubular necrosis. Reflective of the nature of AIN is that the injury from the hypersensitivity reaction was specific for renal interstitium instead of tubules. SPE B is potentially allergenic and may confuse the clinicians due to its clinical mimicry of drug-induced AIN. Although very rare, AIN might be included into the differential diagnosis of patients with streptococcal sepsis and acute renal failure.

Keywords: interstitial nephritis; renal failure; *Streptococcus*

Introduction

Acute interstitial nephritis (AIN) was first described as a 'cellular and fluid exudation in the interstitial tissue' by Councilman in 1898. This venerable treatise illustrated the pathogenetic link between AIN and a septic state with beautifully hand-drawn images according to the kidneys of patients dying of scarlet fever and diphtheria [1]. Over 100 years have passed since Councilman recognized interstitial nephritis as a distinct disease entity, but no study to date has further demonstrated the pathogenesis by detection of streptococcal exotoxins in renal interstitium.

Streptococcal toxic shock syndrome is defined as an invasive Group A streptococcal (GAS) infection associated with shock, multiple organ failure, and erythematous rash with subsequent desquamation. Acute renal failure (ARF) is present in almost all patients within <72 h, and some of them require haemodialysis. However, the true aetiology of ARF has not been illustrated in detail and is mostly considered to be sepsis-related ischaemic acute tubular necrosis without kidney biopsy. Herein, we report an exceptional case of ARF fulfilling the diagnostic criteria of GAS toxic shock syndrome with biopsy-proven AIN.

Case report

A 22-year-old, previously healthy man experienced an episode of sore throat, diarrhoea and general myalgia for 1 week before admission. He sought medical help, and acetaminophen was initially prescribed. Antibiotic and non-steroidal anti-inflammatory drug (NSAID) exposure was denied. As the symptoms deteriorated, he was admitted due to high fever and chills. On the day of admission, his blood pressure was 80/38 mmHg, heart rate 144 beats per minute, respiratory rate 20 breaths per minute and temperature 38.5°C (101.3°F). Physical examination disclosed injected throat and erythematous rash over the trunk, but was otherwise unremarkable. Biochemical studies revealed the following: serum creatinine, 4.8 mg/dL (424.3 µmol/L); urea nitrogen 32 mg/dL (11.4 mmol/L); and serum sodium, 130 mEq/L (130 mmol/L). The haemoglobin level was 16.9 g/dL (169 g/L), platelet count $8.6 \times 10^3/\mu\text{L}$ ($8.6 \times 10^9/\text{L}$) and white blood cell count $19.3 \times 10^3/\mu\text{L}$ ($19.3 \times 10^9/\text{L}$). Urinalysis showed a 3+ positive for urine protein, 167 white

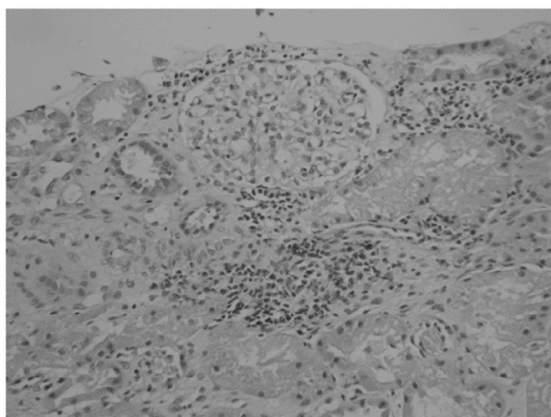


Fig. 1. Haematoxylin and eosin-stained section shows inflammatory cells infiltration and oedema in the interstitium of cortex. All glomeruli were intact without mesangial hypercellularity or matrix expansion. Neither tubular epithelial cell shedding nor interstitial fibrosis were seen (original magnification $\times 100$).

blood cells and 83 red blood cells per average high-power field. The blood culture grew Group A *Streptococcus pyogenes*, but the urine culture result disclosed an insignificant growth. As the generalized skin rash faded, desquamation occurred, especially on the palms and lip. The serologic tests were all within normal ranges such as antinuclear antibody, C3, C4, anti-neutrophil cytoplasmic antibodies, anti-human immunodeficiency virus antibody, markers for hepatitis B and C, and rapid plasma reagin for syphilis. Although the haemodynamic condition soon stabilized, his renal function and urine output still deteriorated. The patient underwent four sessions of haemodialysis from the fifth day of hospitalization because of lung oedema refractory to diuretic therapy. The peak serum creatinine was 16.6 mg/dL (1441.0 $\mu\text{mol/L}$). Under supportive medical care and infection control with ceftriaxone, his renal function recov-

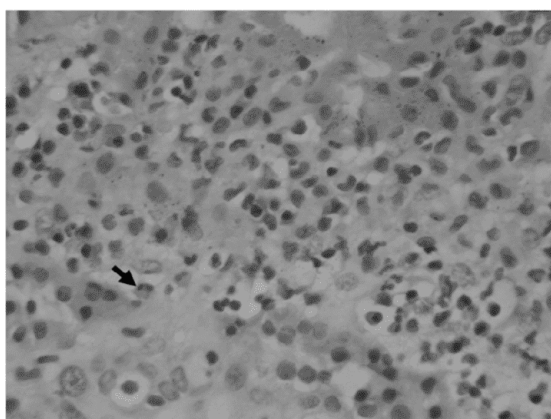


Fig. 2. The oedematous interstitium is infiltrated by admixed inflammatory cells, including neutrophils, lymphocytes, plasma cells and especially eosinophils (black arrow). Scattered eosinophils corresponded to the typical presentation of hypersensitivity reaction in acute interstitial nephritis (haematoxylin and eosin, original magnification $\times 100$).

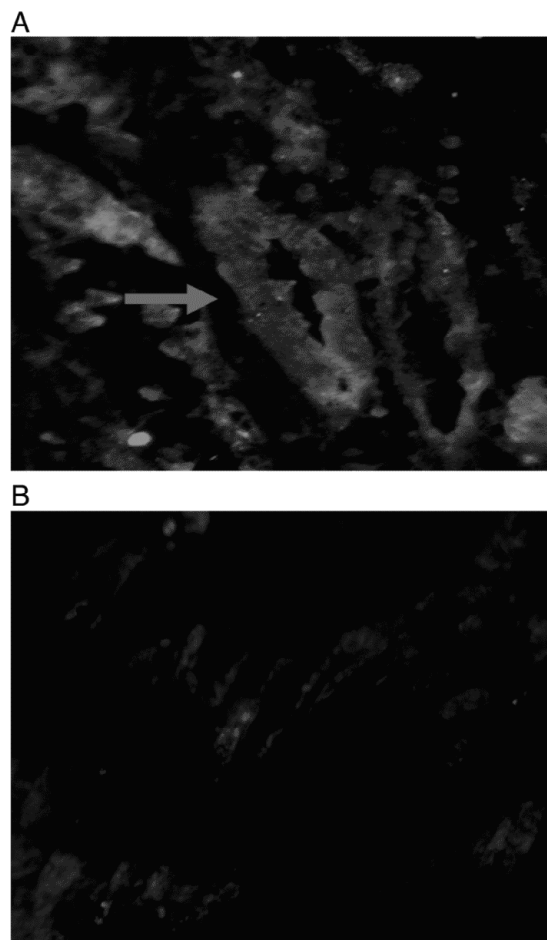


Fig. 3. (A) The IHC study depicted diffuse strong positive signals of anti-SPE B monoclonal antibodies (obtained from Prof. Y-S Lin and Y-H Luo, Ph.D.) in tubular epithelial cytoplasm (red arrow) and renal interstitium of cortical tissue. The fixed cortical tissue was embedded in paraffin and sliced into 4-mm-thick sections. After the fixed tissue sections had been deparaffinized, they were incubated in the retrieval buffer (MARK2 buffer, Serotec Ltd, Oxford, UK) at 92°C for 10 min. The tissue sections were blocked using 10% BSA/PBS, and then using 1 mol/L of NH_4Cl to reduce autofluorescence before adding the primary antibody. Monoclonal anti-SPE B antibody (clone 9C, 10 $\mu\text{g/mL}$) was diluted (1:200) with antibody diluents (DAKO Corporation, Carpinteria, CA, USA), then applied to the sections and incubated at 4°C overnight. The sections were washed in 0.05% PBS-Tween-20 and then incubated with fluorescein isothiocyanate-conjugated goat anti-mouse IgG antibody (Jackson Immuno-Research Laboratories Inc., West Grove, PA, USA) at room temperature for 1 h. (B) The irrelevant monoclonal antibody of the same class (anti-cysteine protease antibodies) was omitted in sections as negative controls.

ered gradually. After 23 days of hospitalization, he was discharged in a dialysis-free status. During the 3-month follow-up period, his serum creatinine level declined to 1.47 mg/dL (130 $\mu\text{mol/L}$).

Because of ARF with unclear aetiology, a kidney biopsy was performed on the 10th day of hospitalization. On light microscopic examination with haematoxylin and eosin stain, the routine and cryostat sections revealed eight and two viable glomeruli without obsolescence. All glomeruli

were undamaged with unchanged mesangial cellularity and matrix. The blood vessels were unremarkable. Neither tubular epithelial cell shedding nor interstitial fibrosis were seen. The interstitium was oedematous and infiltrated by admixed inflammatory cells (Figure 1), including lymphocytes, neutrophils, plasma cells, and especially eosinophils (Figure 2). The tissue submitted for direct immunofluorescence consisted of six glomeruli. The immunofluorescence staining revealed no significant deposition for immunoglobulin G, immunoglobulin A, immunoglobulin M, C3 and C1q. The immunohistochemical (IHC) study depicted diffusely strong positive signals of anti-streptococcal pyrogenic exotoxin B (SPE B) antibodies in tubular epithelial cells and tubulointerstitial compartments of the cortical tissue. Details of our IHC technique were described in Figure 3A. An anti-cysteine protease antibody was used as the negative control (Figure 3B). Conclusively, the final diagnosis was AIN with admixed eosinophils suspicious for being SPE B-induced.

Discussion

A myriad of case reports of infection-related AIN have been published, but so far, none of them could detect the pathogen or toxin in the kidney. GAS infection is also known to be a causative factor of AIN. GAS produces a large number of extracellular products including streptolysin S and O toxins, and pyrogenic exotoxins A, B and C, as well as streptokinase, DNase and protease. The pyrogenic exotoxins, previously known as erythrogenic toxins, cause a hypersensitivity reaction [2], including scarlet fever rash and probable AIN.

SPE B is a cysteine protease and functions as zymogen, which is initially expressed as a 40-kDa ProSPE B and subsequently converted to a 28-kDa active protease by several host factors, such as fibronectin, the interleukin-1 β precursor to the active form, etc. In addition, antibody titres of SPE B were higher than other GAS antigens, including streptolysin O, DNase B, and hyaluronidase in acute post-streptococcal glomerulonephritis (APSGN) patient sera [3]. SPE B may play a role in AIN through its highly potent immunostimulatory effects making it an important virulence factor [4–7]. Nonetheless, the literature to date has not reported the pathogenesis between pyrogenic exotoxins and AIN. In this case, AIN associated with interstitial SPE B deposition was proved by controlled IHC study. Because necrotic debris and cast material will often stain non-specifically for any antibody applied to the tissue, we used an irrelevant monoclonal antibody of the same class (anti-cysteine protease antibodies) as the negative control in this case.

The diagnosis of SPE B-associated AIN was established for the following reasons: First, neither tubular necrosis nor glomerular abnormality were seen in renal biopsy specimen despite hypotension and streptococcal infection. Second, the patient presented sterile pyuria, erythematous rash and renal failure on admission before exposure to antibiotics and NSAIDs. Third, compared with the negative control, the strong positive staining of anti-SPE B antibodies in tubulointerstitial compartments suggested the

association of SPE B and AIN. Last, but not least, both the intact tubular epithelial cells and oedematous interstitium had strong positive signals in IHC staining, whereas only interstitial inflammation was predominant without tubular epithelial cell shedding or necrosis. This reflects the nature of AIN in that the injury of the hypersensitivity reaction was specific for renal interstitium instead of tubules.

SPE B and its precursors had been detected in renal interstitium in previous studies [8,9]. SPE B may cause tubulointerstitial damage via T-cell proliferation and cytokine production [10]. In contrast to complement activation and leucocyte infiltration in the model of APSGN [3], the pathological changes in this case illustrated the typical pictures of AIN without significant glomerular reaction or tubular necrosis. Therefore, we speculate that the deposition of SPE B in the tubulointerstitial compartments induces an inflammatory response specific to renal interstitium. Although further immunologic and molecular studies are needed to confirm our speculation, the same causal agent and characteristics are difficult to reproduce again from the experimentally inoculated and infected host due to the idiosyncratic allergic response in AIN.

Streptococcal infection-associated ARF is most commonly considered to be sepsis-related ischaemic acute tubular necrosis or APSGN. Nonetheless, the therapeutic strategy of AIN was directed towards withdrawal of the offending medication and elimination of the infection, as well as supportive care [11]. We deem it a very important teaching point that early conclusive diagnosis and proper management contribute to better outcome.

In summary, this case alerts us that the possible rare cause of renal failure in streptococcal infection-related AIN may be neglected and underdiagnosed. For the cases of streptococcal infection-associated ARF, early renal biopsy with anti-SPE B stain is perhaps helpful for differential diagnosis. SPE B has a potential allergenic effect, and therefore, the clinician may confuse it with drug-induced AIN. Whether or not to discontinue the offending drugs is a rather important decision, especially in the case of crucial antibiotics. Although very rare, GAS-associated AIN might be included into the differential diagnosis for patients with GAS infection and ARF.

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Conflict of interest statement. None declared.

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Focal segmental glomerulosclerosis as a complication of hepatitis B virus infection

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Abstract

Human hepatitis B virus (HBV) is well known as a cause of membranous nephropathy (MN). While the association of HBV infection with MN is strong, data regarding its association with other glomerular diseases are conflicting. Here, we report a case of focal segmental glomerulosclerosis (FSGS) with HBV infection. In this case, we have found HBV-DNA in urinary podocytes by real-time PCR methods. After the administration of anti-viral therapy, FSGS improved, paralleling the decreased level of HBV-DNA in podocytes. The refractory FSGS induced by HBV could be effectively treated with appropriate anti-viral agents.

Keywords: anti-viral therapy; focal segmental glomerulosclerosis; human hepatitis B virus

pathy, may appear in persons chronically infected with HBV [1]. HBV is well known as a cause of membranous nephropathy (MN). Several morphological forms of renal disease including MN, membranoproliferative glomerulonephritis (MPGN), IgA nephropathy and rarely focal segmental glomerular sclerosis (FSGS) have been described in association with HBV infection. While the association of HBV infection with MN is strong, data regarding its association with other glomerular diseases are conflicting [1,2].

We report herein a case of FSGS with immunotolerated perinatal HBV infection. It was known that the key event in the pathogenesis of FSGS is podocyte injury [3]. In this case, we have found HBV-DNA in podocytes using real-time PCR methods. After the administration of anti-viral therapy, FSGS improved, paralleling the decreased level of HBV-DNA in podocytes.

Introduction

A variety of extrahepatic manifestations, one of the commonest being hepatitis B virus (HBV)-associated nephro-

Case report

A 33-year-old man was admitted to a hospital because of severe peripheral oedema. Laboratory data showed hypo-

Progress in Tuberous Sclerosis Complex Renal Disease

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ABSTRACT: Tuberous sclerosis complex (TSC) is an autosomal dominant disorder that affects both fetal development and postnatal tissue growth, resulting in altered brain structures and a tumor predisposition syndrome. Although every organ system is affected by the disease, kidney involvement is a leading cause of death in adults with TSC. Over the past decade, significant progress has been made in understanding the renal disease. This review focuses on the cystic and solid renal lesions in TSC, including their pathobiology and treatment.

KEY WORDS: TSC, angiomyolipoma, renal cysts, extracellular vesicles, cell nonautonomous trait, renal cell carcinoma, fat poor

I. INTRODUCTION

Tuberous sclerosis complex (TSC), an autosomal dominant disorder, affects both fetal development and postnatal growth, potentially leading to proliferative lesions throughout the body. The birth incidence of TSC is approximately 1 of 5,800,¹ resulting in over one million affected patients worldwide.^{2,3} The condition may not be appreciated by the less-informed clinician as fewer than 40% of patients have the characteristic facial angiofibromata, developmental delay, and intractable epilepsy.⁴ Furthermore, half of TSC patients experience behavioral disorders such as autism or cognitive impairment.⁴ Highlighting the important role of the kidneys, approximately 40% of adult patients with TSC have decreased renal function,⁵ and TSC-associated renal disease is the most common cause of death in adults with TSC.^{6,7} The exact number of TSC patients that go on to dialysis is unclear, in part because TSC is a rare disease and not always available as a diagnosis code for end-stage renal disease databases.

Tuberous sclerosis complex is caused by mutations in two gene loci: the *TSC1* gene located on chromosome 9, which encodes hamartin, and the *TSC2* gene located on chromosome 16, which encodes tuberlin and is adjacent to the *PKD1* gene.

Tuberlin and hamartin cooperate to help regulate the activity of the mechanistic target of rapamycin complex 1, to modulate anabolism and catabolism and thus regulate cell size, growth, migration, and proliferation. Autosomal dominant polycystic kidney disease (ADPKD) is caused by mutations in either the *PKD1* or *PKD2* gene, encoding polycystin-1 and the transient receptor potential channel polycystin-2, respectively. Together, polycystin-1 and polycystin-2 form a receptor–ion channel complex in primary cilia; these proteins also can be found in extracellular vesicles.^{8–10} Although the transient receptor potential channel function of polycystin-2 is understood, the function of this complex, especially the role of polycystin-1, is largely unknown.⁹

Identification of the *TSC2* gene locus was facilitated by the study of a family with ADPKD due to a translocation involving the *PKD1* gene. The *TSC2* gene was discovered because the proband had both ADPKD and TSC associated with the inheritance of an unbalanced translocation.¹¹ Although both the TSC loci gene products interact to regulate the mTORC1 pathway activity, the renal disease is more severe when associated with the *TSC2* gene.

Tuberous sclerosis complex renal disease exhibits three major phenotypes: angiomyolipomata, renal cystic disease, and renal cell carcinoma.

These phenotypes are not exclusive, meaning some patients can have a combination of angiomyolipomata and cysts or, rarely, all three. These renal manifestations are listed in decreasing order of frequency, such that approximately 70–80% of patients will have angiomyolipomata, about 50% will have renal cystic disease, and a very rare TSC patient will have a diagnosis of renal cancer or oncocytoma.

II. ANGIOMYOLIPOMATA

A. Clinical Manifestations

Renal angiomyolipomata were described at least by 1900¹² as a large renal tumor composed of what appeared to be mature white fat, smooth muscle cells, and blood vessels.¹³ Over the last 120 years, it has become clear that the ratio of these elements varies widely. About 30% of patients with TSC seen at a single TSC Center of Excellence with specialized nephrology have significant components with only microscopic fat, if any, truly earning the “fat-poor” moniker.¹⁴

Angiomyolipomata are very common in TSC, and their presence is considered a major criterion for diagnosis.¹⁵ A recent analysis of 80 Belgian children with TSC revealed a median age of 0.8 years at first presentation and median follow-up of 10.2 years. In this population, 75% had renal manifestations.¹⁶ Other studies corroborate that about 80% of affected children,¹⁷ and all adult postmortem samples have renal disease, most commonly renal angiomyolipomata and cysts.¹⁸ About 70% of angiomyolipomata continue to enlarge in the adult population.⁵ Because the disease worsens or can be improved with treatment, disease staging criteria have been established (Table 1).

The renal disease in TSC patients is a significant cause of chronic kidney disease. Among the general United Kingdom population, 40% of patients with TSC have chronic kidney disease (CKD) stage 3 or greater even without a history of angiomyolipomata hemorrhage or surgical interventions.⁵ TSC-associated renal disease has been reported to be the most common cause of death in adults with TSC.^{6,7} A recent paper found that 7.5% of the children with TSC developed end-stage renal disease during the study.¹⁶ In the adult TSC population, renal surgery was very strongly associated with the need for renal replacement therapy, and the combination of renal cysts and angiomyolipomata seemed to put patients at greater risk of renal failure than did either lesion alone.¹⁹

Beyond renal failure, a significant renal risk that TSC patients experience is the risk of angiomyolipomata hemorrhage. Prior to the use of mTORC1 inhibitors, the risk of hemorrhage was between 25% and 50%.¹³ The risk of hemorrhage now appears to be greatly reduced if the patient is maintained on an mTORC1 inhibitor.²⁰

B. Pathobiology

1. Genetic Aspects of Disease

Significant progress has been made on determining the genetic mechanisms at play in TSC-associated angiomyolipomata. TSC-associated angiomyolipomata are thought to be phenotypically expressed by a second somatic mutation or “second hit” silencing the TSC non-mutant allele.²¹ A similar mechanism has been put forward for the cystic disease in both TSC and ADPKD, although the supporting evidence for this mechanism is less robust.^{22,23} One locus for both TSC and ADPKD is on chromosome 16,

TABLE 1: Stages of angiomyolipomata*

Features	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5	Stage 6
Tumor number	0	1 to 4	> 5	< 5	> 5	> 5	> 5
Tumor size	0	< 3 cm	< 3 cm	1 > 3 cm	2 to 4 are > 3 cm	> 5 are > 3 cm	1 > 5cm
Renal morphology	Normal	Normal	Normal	Intact	Intact	Recognizable	Unrecognizable

*Staging of angiomyolipomata burden considers the number of lesions, their size, and their impact on renal structure.

specifically the *PKD1* and the *TSC2* loci. These loci account for about 70–80% of patients with ADPKD or TSC, respectively, and disease associated with these genes is more severe than that associated with *PKD2* or *TSC1*. The *PKD1* and *TSC2* genes are adjacent in a tail-to-tail orientation. This configuration is important because intron 21 of the *PKD1* gene contains a polypurine•polypyrimidine tract that can adopt alternative DNA conformations.²⁴ This odd tract interferes with DNA replication in a polar fashion causing DNA double-strand breaks, facilitating mutagenesis.^{25,26} Synergizing with this DNA damage, the renal osmolality inhibits DNA damage recognition,^{27–29} creating the “perfect storm” for potential somatic mutation.

2. Cell Biology

Angiomyolipomata belong to the perivascular epithelioid cell tumor (PEComa) family of tumors and exhibit both smooth muscle and melanocytic differentiation characteristics.^{30,31} Histologically, angiomyolipomata contain abnormal blood vessel wall architecture surrounded by muscle-like perivascular cells and adipocyte-like cells. The interaction of the mTORC1 pathway with the microphthalmia-associated transcription factor (MITF) family helps to explain why angiomyolipomata express the melanotic marker PMEL (premelanosome protein, also known as SILV, gp100), the antigenic target for the diagnostic human melanoma black (HMB)-45 antibody.³² This associated MITF/TFE transcription factor activity has confounded the diagnostic boundary between TSC-associated renal lesions and translocation renal cell carcinomas (RCCs) and PEComas.³³

Neural crest cells have been posited to contribute to angiomyolipomata because of the co-expression of melanocytic and smooth cell markers.^{34–36} This possibility has been challenged by *TSC2* re-expression experiments in an angiomyolipoma cell line because this introduction changed the expression profile to resemble lymphatic endothelium rather than neural crest-derived tissues.³⁷ A dual knockout of *Tsc2* and *Cdkn2a* in murine epithelial cells altered the cell expression to be somewhat similar to angiomyolipoma when injected into immunocompromised mice.³⁸ However, *Cdkn2a* mutations

are found in melanoma, raising concern over the interpretation of the HMB-45 staining. Mesenchymal stem cell-like cells also have been identified in angiomyolipomata.³⁹ Pericytes may give rise to angiomyolipoma,⁴⁰ and this may explain the association of TSC with vascular aneurysms that arise in angiomyolipomata,⁴¹ aorta,⁶ and brain.⁴²

C. Treatment Modalities

In the past, angiomyolipomata were treated surgically. After such surgical intervention was associated with hastening the loss of renal function,⁶ embolizing the angiomyolipomata one lesion at a time became favored.⁴³ However, about 90% of patients who undergo angiomyolipoma embolization experience a post-embolization syndrome.⁴⁴ Although normally described as fever and pain for days to weeks, embolization does have a risk of severe adult respiratory distress syndrome.⁴⁵ The use of nonsteroidal anti-inflammatory agents can affect coagulation, interfering with the procedure, and affect the renal perfusion. Fortunately, a corticosteroid protocol can abrogate post-embolization syndrome without the other side effects.⁴⁴ Embolization still has issues: the most important is collateral damage to normal renal parenchyma with subsequent loss of renal tissue. Embolization should be used to reduce hemorrhage risk of angiomyolipomata when aneurysms are identified by magnetic resonance or computed topography imaging. Notably, the best size reduction of angiomyolipomata following embolization averages about 50%.⁴⁶

The current international guidelines recommend an mTORC1 inhibitor as the first line of therapy for TSC-associated renal angiomyolipomata.⁴⁷ This recommendation is based on successful therapy with either sirolimus⁴⁸ or everolimus.⁴⁹ This approach also has had a significant, though somewhat unexpected, beneficial side effect: patients treated with mTORC1 inhibitors have a significant reduction in the risk of renal hemorrhage,⁵⁰ and the lesion shrinkage is independent of genotype.⁵¹

While renal allograft therapy with mTORC1 inhibitors has been associated with proteinuria and shortened graft survival, the causes for nephrotic

range proteinuria in these patients are transplant glomerulopathy, recurrence of the underlying disease, and *de novo* glomerulonephritis.⁵² TSC patients treated with mTORC1 inhibitors seem to have mild proteinuria,⁵³ and this has ranged between 4% and 30% in patient series.^{48,49,54–57} Unless the patient had significant proteinuria prior to therapy, the proteinuria appears to remain intermittent or very mild. The renal function in TSC patients treated with mTORC1 inhibitors appears to remain stable or, in a small minority, decline at a rate similar to that prior to therapy in that individual.⁵⁸ There is a decrease in the number of newly emergent adverse effects over time.⁵⁹

III. RENAL CYSTIC DISEASE

A. Clinical Manifestations

In a recent analysis of French patients with TSC, there were almost equal numbers of patients with angiomyolipomata only, angiomyolipomata and cysts, or cysts only.¹⁹ Unfortunately, the health burden of TSC renal cystic disease is underappreciated. Cystic disease can clearly compromise renal longevity. There are five basic patterns of cystic disease (Fig. 1).^{1,60} Stages of the different cystic phenotypes are very helpful in describing progression (Table 2).

Although no FDA-approved treatments of TSC-associated renal cystic disease exist, blood pressure control using angiotensin converting enzyme inhibitors or angiotensin receptor blockers has been adopted, as this approach was effective in the HALT Progression of Polycystic Kidney Disease (HALT-PKD) trial.⁶¹ Small cystic lesions can also

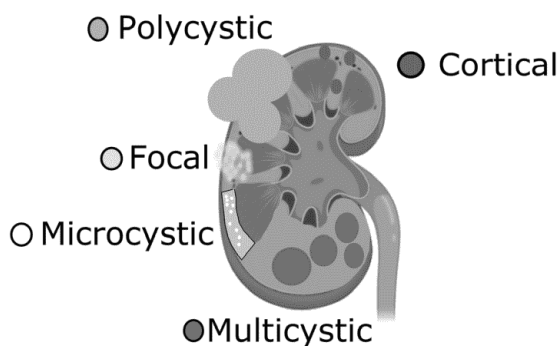


FIG. 1: Five patterns of TSC renal cystic disease. The anatomical location and size of cysts, along with cortico-medullary differentiation, help define the cystic disease patterns. A patient can have multiple patterns. The imaging appearance of multicystic and polycystic disease can be somewhat similar, though polycystic is more severe and is associated with the contiguous deletion of the adjacent *TSC2* and *PKD1* genes.

be mTORC1-responsive.⁶² There are five patterns or TSC-associated renal cystic disease that can occur alone or in combination and these patterns are described below.

TSC polycystic kidney disease accounts for about 2% of TSC renal disease and is associated with a deletion of the adjacent *TSC2* and *PKD1* genes on chromosome 16p13. The imaging appearance is very much like a severe form of ADPKD that is in a very young child. The large cysts do seem to have a more cortical origin—though with their size and distortion, it can be difficult to discern. This pattern of renal cystic disease is associated with a high rate of genetic mosaicism.⁶³ Hypertension can manifest

TABLE 2: Stages of TSC renal cystic disease*

Disease pattern	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5	Stage 6
Polycystic	0	< 2	3 to 6	7 to 10	11 to 20	21–30	> 31
Cortical cystic	0	1 to 10	11 to 20	21 to 30	31 to 40	41–50	> 51
Multicystic	0	1 to 10	11 to 20	21 to 30	31 to 40	41–50	> 51
Focal cystic	0	1 ray	2 ray	3 ray	4 ray	5 ray	> 5 ray
Microcystic	0	10%	20%	30%	40%	50%	> 50%

*Staging of cystic disease accounts for the cystic burden in terms of the amount or extent of disease. A single kidney can have multiple types of cystic disease, which can coexist with renal angiomyolipomata. The disease extents can be quite independent.

in the second week of life or can take several months to develop. These patients almost always become hypertensive.

The lining of these cysts appears to be type A intercalated cell from the cortical collecting duct and to arise from a complex mechanism.⁶² If blood pressure is well-controlled, patients often maintain renal function until they are young adults. Inhibiting mTORC1 in this form of cystic disease will affect only the small cysts and not the large ones. Possibly, mTOR inhibitors can prevent cyst progression if administered before the cysts bud off from the tubules.

TSC microcystic disease exhibits subtle MRI findings in that the renal cortex exhibits increased water signal on T2 sequences, and these findings precede the development of discrete cortical cysts. This pattern of TSC-associated renal cystic disease can be associated with a rapid decline in renal function, with patients developing chronic kidney disease stage 2 or 3 in their late teens or early 20s. Tubular proteinuria may occur as the chronic kidney disease progresses, but hypertension is not common until significant chronic kidney disease develops.

TSC focal cystic kidney disease manifests as a cluster of smaller cysts. The developmental timing can be *in utero*, resulting in an infant with an isolated site with profound cystic disease. The cysts can be expressed during renal healing following acute kidney injury.

Cortical cystic disease is perhaps the most common distinct pattern of TSC cystic renal disease, and the cysts are limited to the cortex and columns of Bertin. This cystic disease occurs when the patient is very young, and initially the cysts are remarkably uniform in size.

TSC multicystic kidney disease exhibits a loss of corticomedullary distinction, and cysts of variable sizes are distributed throughout the cortical and medullary tissue. This pattern can be severe enough that it resembles the polycystic variety but is genetically distinct from the *TSC2/PKD1* contiguous gene syndrome.

B. Pathobiology

Historically, inherited renal cystic diseases are often associated with both the primary cilia, an

organelle thought to be involved in sensing the external environment,⁶⁴ and increased activity in the mTORC1 pathway.^{65,66} These two signaling pathways converge because the primary cilia regulate the mTORC1 activity.^{67,68} Although the polycystic disease-related proteins and primary cilia are mechanistically involved in polycystic kidney disease, they are not sufficient as the “mediator.” The loss of either a polycystin protein *or* the primary cilia structure results in similar renal cystic disease phenotypes. Yet simultaneous inactivation of both the polycystin gene and cilia expression assuage the renal cystic disease severity compared with polycystin-only knockout mice.⁶⁹ This finding suggests that the polycystins modulate an unidentified signaling pathway that requires intact cilia to function. Recent work in a murine ADPKD model supports the notion that this intercellular communication modality may be extracellular vesicles (EVs).⁷⁰ EVs carry cargo, including putative modulators of polycystic disease signaling, such as Hedgehog⁷¹ and Wnt.⁷²

Like the *Pkd* models, murine *Tsc* renal disease models exhibit elevated mTORC1 activity (phospho-S6 expression) in the cystic epithelium, and likewise with a much lower frequency of cells that have lost *Tsc* gene expression.^{73–75} The second hit mechanism for TSC angiomyolipoma is incongruent with this failure to identify significant loss of heterozygosity (LOH) in the TSC cystic epithelium.^{74,76} Cystic epithelium from patients also expresses both tuberin and hamartin.⁷⁷ In contrast, angiomyolipomata clearly exhibit LOH and an absence of tuberin staining.⁷⁷ This low frequency of LOH is also seen in *PKD1*-associated ADPKD, indicating that cystic disease, in general, may exhibit a more complex disease mechanism.^{23,78}

To understand the cystic disease in TSC better, a novel mouse model having the *Tsc2* gene inactivated specifically in principal cells was generated by breeding a *Tsc2^{fl/fl}* mouse to one containing Cre-recombinase driven by the aquaporin-2 promoter. The resulting mice develop significant cystic disease with age.⁶² Although the *Tsc2* gene was deleted in principal cells, the cysts were comprised largely of type A intercalated cells that still contained an intact *Tsc2* gene.⁶² This is also

true if the *Tsc1* gene is disrupted using a similar approach.⁷⁹ Type A intercalated cells are also involved in human TSC-related cystic disease.^{62,79} Murine lineage-tracing experiments revealed that principal cells undergo limited clonal expansion but provide relatively few cells to the overall cyst.⁸⁰

The cystic kidneys expressed significantly more interstitial EVs than non-cystic kidneys did, but cystic mice excreted fewer urinary EVs than did non-affected mice. Extracellular vesicles are lipid-bound structures of varying sizes that are pivotal in intercellular communication because their cargo consists of RNA, protein, lipid, and even DNA and are produced both through the endosomal pathway and by budding from the plasma membrane (Fig. 2).⁸¹ Remarkably, mTORC1 inhibition reduced the interstitial EV production toward normal kidney production levels.⁸⁰ Cystic fluid was also rich in EVs. The loss of the *Tsc2* gene caused the EV-producing cells to yield EVs that altered their effect on the transcriptome of normal renal tubular epithelium compared to EVs generated from isogenic cells with an intact *Tsc* gene.⁸⁰ A similar result was found by using a neuronal *in vivo* assay, where EVs produced from *Tsc1*-deleted cells reprogram the neighboring wild-type cells such that they became similar to *Tsc1*-mutant cells.⁸² Thus, *Tsc2*-null principle cells misdirect genotypically normal intercalated cells via abnormal EV production, inducing them to form cysts.

Primary cilia function as both EV transmitters and receivers.^{83–89} Ciliary EVs have significant implications for renal cystic disease. Primary cilia are expressed on renal tubular principal cells but rarely on intercalated cells.⁹⁰ The targeted disruption of the *Pkd1* gene in principal cells leads to significant renal cystic disease, while such disruption in intercalated cells leads to a muted phenotype.⁹¹ The previously described finding that either the disruption of *Pkd1* or loss of primary cilia result in similar cystic phenotypes, while simultaneous inactivation of *Pkd1* gene and primary cilia result in a less cystic phenotype than that obtained with the *Pkd1* knockout may be evidence for EVs mediating the cystic disease.⁶⁹

C. Treatment Modalities

mTORC1 inhibitors are effective and approved for multiple indications in TSC, such as angiomyolipomata, subependymal giant cell astrocytoma, seizures, and lymphangioleiomyomatosis.^{48,49,57,92,93} Unfortunately, TSC cystic disease does not have an approved therapy, so only the consequences of cystic disease, such as hypertension and chronic kidney disease, are targeted for therapy. Although multiple preclinical studies demonstrated an effect on cystic disease, the use of mTORC1 inhibitors for adults with autosomal dominant polycystic kidney disease failed to demonstrate benefit.^{94,95} This outcome may be due to the fact that large cysts are believed to be detached from the tubule, representing a mass lesion independent from the lesions in the murine models.⁹⁶ Patients with TSC cortical cystic disease, with smaller cysts that are still connected to the tubule, do respond to mTORC1 inhibition and remodel below the MRI threshold.⁹⁷ As mentioned above, pericytes may be a critical cell type in angiomyolipoma biology.⁴⁰ Disrupting the *Tsc* gene in pericytes, likewise, can result in renal cystic disease thought to be mediated by EVs.⁹⁷ This interesting feature may help explain the coexistence of cystic disease and angiomyolipomata in the literature,⁹⁸ as pericytes do appear to facilitate cyst growth.^{62,99}

IV. RENAL CELL CARCINOMA

A. Clinical Manifestations

The association between TSC and a risk for renal cell carcinomas (RCCs) has an accepted overall prevalence of 2–4%.¹⁰⁰ The increased risk appears to affect patients younger than 50 years.¹⁰¹ However, this is complicated, as a recent systematic analysis of TSC-associated malignancies revealed that the prevalence of all malignant tumors in this group was comparable to the prevalence in the general population (5.6%, 95% CI 2.99 ± 9.31%, vs. 4.4%) although the median age at cancer diagnosis was lower in the TSC-associated malignancy group (37.5 years, 95% CI 28.6–44.7, vs. 66.0 years).¹⁰² Two patients (13.3%) died of their

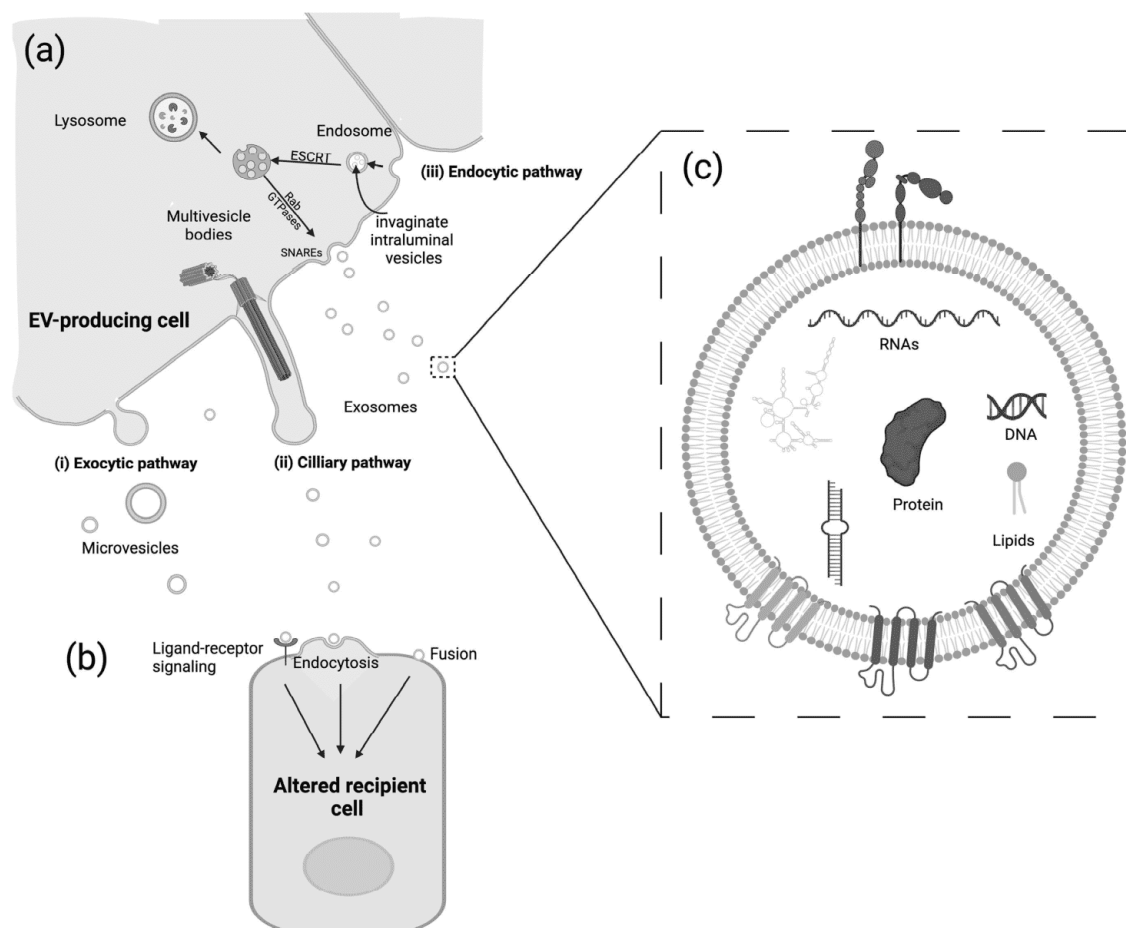


FIG. 2: Schematic diagram of EV biology. (a) As seen in the schematic in the EV-producing cell, EVs are produced by three mechanisms. (i) The first pathway, the exocytic system, uses ceramide synthesis to induce vesicle curvature and budding.¹¹⁶ This can result in large extracellular vesicles sometimes called microvesicles. (ii) There is ample evidence of primary cilia-related proteins being EV cargo, but the exact mechanism of renal epithelial primary cilia EV production and contribution to the tissue EV pool is unknown.^{117,118} (iii) The third mechanism uses tetraspanin to organize specific proteins, such as premelanosome protein (PMEL), to drive vesicle formation.^{119,120} The PMEL protein is the target of the antibody HMB-45 used to identify TSC-associated angiomyolipomata and can stain microscopic cysts in TSC.¹²¹ The mechanism uses endosomal sorting complex required for transport (ESCRT) machinery, consisting of four protein complexes (ESCRT-0, -I, -II, and -III) along with accessory proteins (Alix, VPS4, and VTA-1).¹²² During the process of early endosome maturation into multivesicular bodies, the endosomal membrane invaginates to form the invaginate intraluminal vesicles in the lumen of EV-producing cells, which is mediated by the ESCRT machinery. The multivesicular body can fuse with cell membrane and release ILVs as extracellular vesicles, sometimes referred to as exosomes, or fuse with the lysosome to degrade the contents. Members of the Rab GTPases, SNAREs, and synaptotagmin families play critical roles in multivesicle body trafficking and extracellular vesicle secretion. (b) The EVs can impact the recipient cell by ligand-receptor signaling or by being internalized by endocytosis or membrane fusion. (c) These latter two mechanisms release the EV cargo DNA, lipid, protein, and RNA (lncRNA and miRNA) cargo to impact cellular function.

cancers; however, the cancers, a glioblastoma multiforme and an abdominal sarcoma, are not typically thought of as being associated with TSC. The outcome was favorable in the remaining individuals.¹⁰² While the TSC axis is generally thought to be involved in TSC-associated malignancies, it is also possible that the earlier diagnosis in the TSC population is, in part, due to TSC surveillance protocols.

In 2014, two series together reported more than 100 RCC lesions in patients with TSC.^{100,103} The age at onset of cancer was 30–40 years but included pediatric patients as young as 7 years. As seen in other series, most RCCs occurred in female patients. The pathologic features of these tumors included chromophobe-like features and eosinophilia, although some of the tumors were unclassified. As pointed out by Henske et al. in a recent excellent review, the pathologic heterogeneity of RCC in patients with TSC is reminiscent of the pathologic heterogeneity in Birt–Hogg–Dube–associated RCC,¹⁰⁴ which also exhibits chromophobe-like tumors. Henske et al. highlighted that the sporadic counterpart tumors that carry somatic *TSC1/TSC2/mTOR* mutations also exhibit unclassified eosinophilic tumors, eosinophilic solid and cystic RCC, and RCC with leiomyomatous stroma.¹⁰⁴

TSC-associated renal cancer has rarely been associated with fatalities.¹⁰⁵ In one series, four of six patients died from their metastatic disease. Five of the six patients had a clear-cell morphology, with two having high-grade spindle cell areas and one having granular cell histology. One tumor was anaplastic throughout. Five of the tumors in this series were submitted for loss of heterozygosity, with two having loss of heterozygosity on chromosome 9q34 (*TSC1* locus) and one having loss of heterozygosity on chromosome 16p13 (*TSC2* locus). Immunostaining revealed HMB-45–positivity in four of the tumors; HMB-45–positivity is also seen in TSC-associated renal angiomyolipomata, some renal cysts, and pulmonary lymphangiomyomatosis.

In a second series of 57 RCCs from 13 female and 5 male patients with TSC, nine patients (50%) had multiple synchronous and/or metachronous RCCs, and five had bilateral RCCs (28%).¹⁰⁶ Fifteen

patients had clinical follow-up information, all of which showed no evidence of distant metastatic disease from 6 to 198 months after their initial surgery (mean: 52 mo). All of the RCCs that were analyzed revealed a strong nuclear reactivity for PAX8 and exhibited no HMB45 staining.

Analysis of a third series of 46 renal epithelial neoplasms from 19 patients with TSC allowed the authors to divide the tumors into three groups.¹⁰⁰ The largest subset included almost half of the tumors and exhibited a prominent papillary architecture and uniformly deficient SDHB expression, giving rise to the “TSC-associated papillary RCC.” The second subset of tumors had morphological similarities to a hybrid oncocytic/chromophobe tumor (HOCT); the third and smallest subset remained unclassifiable. The TSC-associated papillary RCCs (PRCCs) exhibited prominent papillary architecture that was lined by clear cells. These 19 patients were also free of distant metastasis, and none died.

B. Pathobiology

Although the precise pathobiology of TSC-associated RCC remains an enigma, it may be linked to TSC-associated renal cystic disease. The Eker rat model and a host of mouse *Tsc* models demonstrate cysts and the development of renal cancers.¹⁰⁷ A recent new mouse model used a principal cell-specific recombinase system to disrupt either *Tsc1* or *Tsc2*. In either situation, the cysts were largely composed of genetically intact intercalated cells.^{79,80,97,108} The mice are born with normal kidneys and develop cystic disease that can also have papillary lesions by 19 weeks. By 25 weeks, all the cystic lesions seem to have a proliferative response and even appear to exhibit papillary renal cell carcinoma lesions, even with rhabdoid features.⁸⁰ These findings raise the possibility that these normal cells are being conscripted into the pathological process. We posit that these changes are driven by EVs.^{109,110} This sort of cell nonautonomous disease trait is not new in the cancer field, and a role for EVs in cellular reprogramming has been observed in a targeted mouse model that inactivated *Brcal*. Using targeted *Brcal* in mouse

ovarian granulosa cells, Chodankar et al. induced cystic tumors with genetically intact *Brcal* genes in the ovaries and uterine horns. The authors hypothesized that the loss of *Brcal* by granulosa cells caused them to secrete something that caused the tumor to arise in a different cell type.¹¹¹ We posit that the mutant granulosa cells secreted EVs that led to the tumors arising in the uterine horns. The role of EVs in renal cell carcinoma has recently been reviewed.¹¹²

C. Treatment Modalities

Although resection of the RCC has been the cornerstone of therapy for patients with TSC, the role for mTORC1 inhibitors is clearly of interest. RCC in the general population responds, at least initially, to mTORC1 inhibition, but the RCC biology in those with TSC may differ.¹¹³ Very rarely, the epithelioid angiomyolipoma in the context of TSC can escape mTORC1 inhibition and even have distant metastatic lesions. One preclinical therapy used a model in which C57BL/6J mice were injected with syngeneic *Tsc2*-deficient cells. Because programmed death 1 coinhibitory receptor (PD-1) is upregulated on T-cells in angiomyolipomata, they used antibodies to PD-1 and found a reduction of *Tsc2*-deficient cells.¹¹⁴ This approach has also been used in a patient and resulted in a durable response.¹¹⁵

V. CONCLUSIONS AND IMPLICATIONS

Tuberous sclerosis complex renal disease exhibits diverse forms but offers a unique possibility for therapeutic advance. The role of EVs in amplifying the pathogenic potential of the second, somatic mutation (or second hit) has several important implications. The pathogenic role for EVs in TSC renal cystic disease may imply a role for this intercellular communication in the other forms of TSC renal disease, such as renal cell carcinoma and angiomyolipomata, as well as disease in other organ systems, such as pulmonary lymphangioleiomyomatosis and cardiac rhabdomyomata. Understanding EV biosynthesis, trafficking and EV docking, and EV cargo could open

significant new inroads into therapies and preventative treatments.

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