Justus-Liebig-Universität Gießen

Fachbereich Medizin

Medizinisches Zentrum für Chirurgie, Urologie und Anästhesiologie

Klinik für Allgemein-, Viszeral-, Thorax-, Transplantations- und Kinderchirurgie

Klinikdirektor: Prof. Dr. W. Padberg

Untersuchungen zu aktuellen pathomechanistischen und therapeutischen Aspekten der akuten Appendizitis

Habilitationsschrift

zur Erlangung der Lehrbefähigung für das Fach Viszeralchirurgie

im Fachbereich Medizin der Justus-Liebig-Universität Gießen

vorgelegt von

Dr. med. Alexander Reinisch-Liese

Gießen 2022

Verzeichnis der Anlagen

Anlagen sind in der Reihenfolge aufgeführt, in der sie im Weiteren bearbeitet werden.

A. Reinisch, J. Heil, G. Woeste, W.O. Bechstein, J. Liese. The meteorological influence on seasonal alterations in the course of acute appendicitis. *J Surg Res*. 2017. doi: 10.1016/j.jss.2017.05.015 . IF 2,051

A. Reinisch, P. Malkomes, N. Habbe, W.O. Bechstein, J. Liese. Bad Bacteria in Acute Appendicitis: rare but relevant. *Int J Colorectal Dis*. 2017. doi: 10.1007/s00384-017-2862-0. IF 2,533

A. Reinisch, S. R. Schröder, W. Padberg, F. Ulrich, J. Liese. Antibiotic-treated Acute Appendicitis – Reception in Social Media. *Langenbecks Arch Surg.* 2019. doi: 10.1007/s00423-019-01777-y. IF 2,184

A. Reinisch, M. Reichert, A. Hecker, W. Padberg, F. Ulrich, J. Liese. Non-operative, antibiotic treatment of appendicitis in adults – a survey among clinically active surgeons in Germany. *Visc Med*. 2020. doi: 10.1159/000506058. IF 1,96

A. Reinisch, M. Reichert, C. C. Ondo Meva, W. Padberg, F. Ulrich, J. Liese. Frailty in Elderly Patients with Acute Appendicitis. *Eur J Trauma Emerg Surg.* 2022. doi:10.1007/s00068-022-01878-2. IF 2,374 (IF 2021)

Inhaltsverzeichnis

Gendererklärung

In der vorliegenden Habilitationsschrift wird zur Wahrung einer besseren sprachlichen Lesbarkeit das generische Maskulinum verwendet. Sämtliche Bezeichnungen beziehen sich dabei grundsätzlich gleichermaßen auf alle Geschlechter. Diese Sprachform beinhaltet keine Wertung.

Abkürzungen

AA	akute Appendizitis
AUC	Area Under the Curve
CD	Clavien-Dindo-Klassifikation
CRP	C-reaktives Protein
DNS	Desoxyribonukleinsäure
DRG	Diagnosis Related Groups; diagnosebezogene Fallgruppen
EAES	European Association for Endoscopic Surgery
ESKAPE	Enterobacteriacae, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumanii, Pseudomonas aeruginosa, Enterokokken
HFRS	Hospital Frailty Risk Score
IND	Individuen
KI	Konfidenzintervall
MALT	Mukosa-assoziiertes lymphatisches Gewebe
mFI	modified Frailty Index
ORG	Organisationen
RET	Rezeptor-Thyrosinkinase
ROC	Receiver Operating Characteristic
SD	Standardabweichung
Sek	Sekunde
SSI	Surgical Site Infection
VRE	Vancomycin-resistente Enterokokken
WSES	World Society of Emergency Surgery

1. Einleitung

Die akute Appendizitis ist wie kaum eine andere Erkrankung mit der Allgemein- und Viszeralchirurgie verbunden. Die Operation des entzündeten Wurmfortsatzes ist ein Eingriff, der auch außerhalb medizinischer Fachkreise als nahezu exemplarisch für die chirurgische Therapie akuter Erkrankungen des Bauchraums wahrgenommen wird. Für viele angehende Chirurgen ist die Appendektomie die erste "richtige" Bauchoperation, welche diese durchführen.

Im Kontrast hierzu steht, dass bei fundamentalen Aspekten der Erkrankung, beispielsweise bezüglich der Pathogenese, noch große Wissenslücken bestehen. Weder hinsichtlich der Ursache bzw. möglicher Auslöser der akuten Appendizitis besteht Klarheit, noch sind viele der Faktoren, welche den Verlauf der Erkrankung bestimmen, verstanden. Der erste Schwerpunkt meiner Forschung war deshalb, mögliche Faktoren, welche die Erkrankung und ihren Verlauf beeinflussen, zu untersuchen.

Hinsichtlich anderer Punkte, insbesondere zu diagnostischen Verfahren, liegen inzwischen solide Kenntnisse auf Basis auch aktueller Forschungen vor. Ein differenziertes diagnostisches Vorgehen unter Nutzung von Scores, der Bildgebung und Algorithmen findet zunehmend Verbreitung in der Krankenversorgung [1].

Die therapeutischen Optionen der Appendizitis sind bei genauerer Betrachtung komplexer als häufig angenommen wird. Therapie der Wahl war und ist seit über hundert Jahren die Appendektomie. In Konkurrenz hierzu steht, aktuell im Fokus, die nichtoperative, antibiotische Behandlung der Appendizitis, mit der auch ich mich, wie später noch ausführlich dargestellt, wissenschaftlich beschäftige.

Die Appendizitis erfährt darüber hinaus, analog zur zunehmenden Alterung der Bevölkerung, einen demographischen Wandel. Während lange die Appendizitis als eine Erkrankung des jungen Erwachsenen wahrgenommen wurde, beobachtet man zunehmend mehr Appendizitiden beim älteren Menschen mit ungünstigen Verläufen [2]. Dies hat mein Interesse an diesem Aspekt der Erkrankung geweckt und mich zur Durchführung meiner fünften in dieser Zusammenfassung dargestellten Studie veranlasst.

Die Genese der Appendizitis ist, wie bereits angedeutet, nicht abschließend verstanden. Als eigenständige Erkrankung er- und bekannt ist die Appendizitis seit Anfang des 19. Jahrhunderts. Insbesondere der Umstand, dass die putride Entzündung im rechten Unterbauch von der Appendix vermiformis ausgeht, nicht etwa vom Coecum, fand erst nach 1842 Anerkennung und war zeitweise umstritten [3]. Dies ist möglicherweise ein Grund dafür, dass die Erkrankung im deutschen Sprachraum umgangssprachlich auch weiterhin als „Blinddarmentzündung", also Entzündung des Coecums, bezeichnet wird [3]. Nachdem klar wurde, dass die Entzündung von der Appendix vermiformis ausgeht, konnte untersucht werden, was die Pathologie auslöst. Lange bestand die Theorie, dass ein Kotstein zur Lumenobstruktion mit folgender Dilatation, Gangrän und Perforation der Appendixspitze führt. Zurückzuführen ist diese Vorstellung wohl auf den Londoner Chirurgen James Parkinson (1755-1825). Parkinson veröffentlichte als einer der ersten Ärzte der Neuzeit den Bericht einer tödlich verlaufenden, perforierten akuten Appendizitis bei einem Fünfjährigen und beobachtete hier: „[...] Upon opening the appendix, a piece of hardened faeces was found impacted in that part of it which lay between the opening and that portion of the appendix, which was not evidently marked by disease" [4]. Die akademischen Chirurgen des 19. Jahrhunderts machten ähnliche Beobachtungen und publizierten pathogenetische Theorien, welche die Fremdkörper-Hypothese stützten [5, 6].

Bis weit in die zweite Hälfte des 20. Jahrhunderts wurde diese pathogenetische Hypothese wenig hinterfragt. Zunehmend fiel jedoch auf, dass eine durch Fremdkörper oder durch Kotsteine bedingte Lumenobstruktion nur bei einem kleinen Teil der Appendizitiden vorliegt. Somit erfuhr die Erforschung von Faktoren, welche Pathogenese und Krankheitsverlauf der Appendizitis beeinflussen wieder mehr Aufmerksamkeit. Es gerieten infektiologische Aspekte als Ursache bzw. wesentlicher (Ko-)Faktor der Appendizitis in den Fokus, wenn auch bislang ohne eindeutige Ergebnisse [7-9]. Die Beobachtung ethnischer Unterschiede der Appendizitisraten und familiärer Häufung ließen genetische Faktoren vermuten, zugleich fanden sich aber auch Berichte über den Einfluss der Jahreszeiten, Ozonwerte oder Umweltverschmutzung auf die Entstehung und den Verlauf der Appendizitis [10]. Auch ich beschäftigte mich mit diesem Themenkomplex: Meine Untersuchungen zeigten hierzu einen Einfluss meteorologischer Einflüsse auf den Krankheitsverlauf.

Krankheitsauslöser bzw. Krankheitsursache und der Krankheitsverlauf können bei der akuten Appendizitis in Teilen getrennt betrachtet werden. Dies gilt insbesondere für die Rolle der Bakterien im Krankheitsprozess. Die Appendix vermiformis ist ein Reservoir für Bakterien: Das Mikrobiom der Appendix besteht aus hunderten bis tausenden verschiedener Bakterienpopulationen, eine klare Abgrenzung zum Mikrobiom des Kolons, speziell des Coecums, ist nicht möglich [11, 12]. Wie auch im Kolon kann diese mikrobielle Flora nicht als pathogen per se angesehen werden. Das Mikrobiom der Appendix spielt, wohl zusammen mit dem Mukosa-assoziierten lymphatischen Gewebe (MALT) der Appendix eine wichtige immunmodulatorische Rolle: Dies lässt sich unter anderem aus mutmaßlichen Zusammenhängen zwischen einer Appendektomie und entzündlichen Darmerkrankungen, Clostridium difficile Enteritis, aber auch völlig anderen Krankheitsbildern wie z. B. Morbus Parkinson erkennen [13-16].

Die Flora in der Appendix spielt eine Rolle für die infektiöse Genese der Appendizitis. Ob und in welchem Umfang sie ursächlich für die Entzündung ist, bleibt jedoch unklar. Für einige Fälle können spezifische Erreger ausgemacht werden, oft verbunden mit besonderen Verläufen, so zum Beispiel für Yersinien, Actinomyces oder Mycobacteria. Allerdings ist eine solche eindeutige Assoziation zwischen Erreger und Erkrankung eher selten. Ähnliches gilt auch für die viral (Adenoviridae, Cytomegalovirus) oder parasitär (Enterobius vermicularis, Schistosoma haematobium, Entamoeba histolytica) bedingte Appendizitis [7]. In den weitaus überwiegenden Fällen lässt sich bei der Appendizitis eine bakterielle Mischflora nachweisen. Von besonderem Interesse sind hier die Bakteriengruppen, welche bei der Appendizitis möglicherweise Einfluss darauf haben, ob die Appendizitis ulzerös auf die Schleimhaut begrenzt bleibt, ob sie purulent oder phlegmonös wird, oder ob die Appendixwand untergeht und eine gangränöse oder perforierte Appendizitis entsteht. In diesem Zusammenhang konnten zwei Fusobakterienstämme (Fusobacterium nucleatum und necrophorum) identifiziert werden, welche mit einem schwereren Verlauf der Appendizitis assoziiert scheinen. Diese Fusobakterien, welche im gesunden Kolon nicht nachgewiesen werden können, lassen sich bei schwereren Verlaufsformen der akuten Appendizitis bis in tiefe Wandschichten nachweisen. Es scheint sehr wahrscheinlich, dass sie einen entscheidenden Faktor für die Perforation der Appendix darstellen [17]. Das die Rolle von Fusobakterien bislang kaum erfasst wurde, ist wahrscheinlich dem Umstand geschuldet, dass dieses Bakterium sehr schwer kultivierbar ist. Es kann somit bei operativen Abstrichen kaum nachgewiesen werden [18]. Erst die Desoxyribonukleinsäure (DNS)-Sequenzierung aus Proben entzündeter Appendizes

weisen Fusobakterien neben den sonstigen häufigen Erregern, vor allem Enterococcus spp., Bacteriodes spp. und Echerichia coli nach [11]. Letztlich muss noch differenziert werden, welche Bakterien, insbesondere bei der komplizierten Appendizitis, periappendikulär in der freien Bauchhöhle oder in einem perithyplitischen Abszess nachweisbar sind, auch bereits ohne dass es zur Perforation der Appendix gekommen ist. Bei der Perforation der Appendix tritt Darminhalt mit der darin enthaltenden Flora aus und führt zum Abszess oder bei freier Perforation zur Peritonitis. Aber auch bei der putrid-phlegmonösen und der gangränösen, nicht perforierten Appendizitis kommt es zur Kontamination bzw. Infektion der Umgebung der Appendix, möglicherweise durch die Durchwanderung der Appendixwand. Regelmäßig lässt sich eine bakterielle Mischflora mit wiederum verschiedenen gramnegativen Bakterien wie E. coli und Bacterioides spp., bei komplizierten Verläufen auch Streptokokken und Pseudomonaden, nachweisen [19-21]. Diese Bakterien in der Bauchhöhle bzw. in einem Abszess haben mit größter Wahrscheinlichkeit einen entscheidenden Einfluss auf den Verlauf der Erkrankung. Vor dem Hintergrund zunehmender Entwicklung von Antibiotika-Resistenzen ist dieser Bereich der Appendizitis-Forschung von größtem Interesse. Auch bezüglich dieses Komplexes ist eine strikte Abgrenzung zwischen Krankheitsentstehung und -verlauf kaum möglich.
In dieser kurzen Übersicht zu den noch offenen Fragen hinsichtlich der Pathogenese der Appendix soll abschließend noch ein Weg aufgezeigt werden, der die Beobachtungen von vor über 150 Jahren mit aktuellen Erkenntnissen verbindet: Schulz et al. konnten bei Kindern mit Appendizitis Unterschiede in der Verteilung von Rezeptor-Thyrosinkinasen (RET)-Protoonkogenvarianten nachweisen, denen ein Einfluss auf die Peristaltik der Appendix zugeschrieben wird. Somit könnte, genetisch bedingt, eine verminderte Schleim-Clearance zur Bildung lumenobstruierender Fäkolithen führen, was den Kreis zu den initialen pathogenetischen Vorstellungen schließt [22]. All dies bleibt jedoch vage und verdeutlicht den Bedarf weiterer Forschung zur Pathogenese der Appendizitis.

Die nichtoperative, antibiotische Therapie der akuten Appendizitis ist ein weiterer Schwerpunkt meiner Forschung. Die konservative Appendizitistherapie wird seit den 1940er Jahren durchgeführt und wurde 1956 von Eric Coldrey [23] als therapeutisches Konzept definiert. Regelmäßige Anwendung fand diese Therapie jedoch nur bei besonderen Patientenkollektiven oder in speziellen Situationen [24-26]. Nach 2005 erfuhr diese Therapieform gesteigerte Aufmerksamkeit, und in Folge mehrerer hochrangig publizierter Studien in den 2010er Jahren wurde die konservative, antibiotische Therapie der Appendizitis zum „hot topic“ [27-30]. Diese Diskussion erreichte sogar die nichtmedizinische Öffentlichkeit und bis heute wird diese Therapieoption in regelmäßigen Abständen und mit unterschiedlicher Beurteilung in verschiedenen Medien vorgestellt [31, 32].

Es ist nicht klar festgelegt, wann und unter welchen Voraussetzungen ein nichtoperativer Therapieversuch unternommen werden kann. Bedenken bestanden und bestehen hinsichtlich einer möglichen Verschlechterung der Erkrankung durch den Verzicht oder die Verzögerung der etablierten, operativen Therapie. Befürchtet wurde z. B. die Entwicklung einer generalisierten Peritonitis, welche zwingend die notfallmäßige Operation notwendig macht. Um dieses Risiko zu minimieren und der Patientensicherheit gerecht zu werden, beschränken sich die wichtigsten Studien deshalb auf die unkomplizierte, nicht perforierte Appendizitis [27, 28, 30, 33]. Der Ausschluss einer komplizierten Appendizitis erfolgt hierbei häufig durch eine Computertomographie. In der Regel beginnt eine nichtoperative, antibiotische Therapie mit einer zunächst zwei- bis dreitägigen intravenösen Gabe eines Breitspektrum-beta-Laktam-Antibiotikums oder eines Carbapenems, häufig kombiniert mit Metronidazol. Hieran schließt sich eine orale, in der Regel ambulante Therapie an, so dass eine Gesamttherapiedauer von 7-10 Tagen erreicht wird. Klassifiziert wurden in den meisten Studien die primären Therapieversager, d. h. Patienten, die wegen ausbleibender Besserung oder Verschlechterung unmittelbar operiert werden mussten, weiterhin die frühen Therapieversager (OP in den ersten Wochen bzw. im ersten Monat) und die sogenannten Rezidive. Letztere werden in der Regel als Patienten definiert, bei welchen im ersten Jahr nach konservativer Therapie erneut eine Appendizitis auftritt.

Inzwischen liegen Meta-Analysen zum kurz- und mittelfristigen Therapieerfolg und erste Studien mit Langzeitergebnissen zur nichtoperativen, antibiotischen Therapie vor. Bezüglich der Komplikationen bzw. einer befürchteten Aggravation der Erkrankung sind die randomisierten Studien und damit die Meta-Analysen relativ homogen. Eine Zunahme von schweren Komplikationen trat unter antibiotischer, konservativer Therapie nicht auf. Durch die fehlenden intra- und postoperativen Komplikationen, wie z. B. Wundheilungsstörungen, waren die Komplikationsraten in der konservativen Gruppe in einigen Studien sogar niedriger [34]. Hinsichtlich der

Effektivität der Behandlung zeichnet sich ab, dass die antibiotische Therapie initial häufig erfolgreich ist. Allerdings werden etwa 10-20 % der Patienten im ersten Monat und 20-40 % im ersten Jahr nach konservativer Therapie dennoch appendektomiert [33-35]. Die veröffentlichten Langzeitergebnisse nach zwei bzw. fünf Jahren geben Rezidivraten zwischen 40 % und 50 % an [27, 33, 36]. Das somit etwa jedem zweiten Patienten eine Operation erspart werden kann, führt in der Langzeitanalyse von Salminen et al. zu einer signifikanten Reduktion von Schmerzen, Narbenhernien und Verwachsungsbeschwerden nach einem und fünf Jahren [36]. In der Leitlinie der European Association for Endoscopic Surgery (EAES) zur Behandlung der Appendizitis wird die nichtoperative, antibiotische Therapie eher zurückhaltend bewertet, die etwas aktuellere Leitlinie der World Society of Emergency Surgery (WSES) stellt diese Therapieoption in einem eher positiven Kontext dar [37, 38]. Hierbei ist jedoch anzumerken, dass führende Autoren der WSES-Leitlinie selbst große Studien mit positiven Ergebnissen zur konservativen Therapie der Appendizitis veröffentlicht haben und somit ein gewisses Bias besteht.

Grundlegende Änderungen therapeutischer Konzepte ließen sich bereits bei anderen chirurgischen Erkrankungen beobachten: Beispielhaft genannt sei hier die Therapie des Magen- und Duodenalulcus, welches seit Entdeckung von Helicobater pylori und der Entwicklung der Protonenpumpenhemmer überwiegend konservativ behandelt wird. Ob eine alternative bzw. neue Therapieform sich etabliert, ist natürlich entscheidend davon abhängig, ob es der Forschung gelingt, eindeutige Vorteile nachzuweisen. Allerdings ist neben der reinen Evidenzlage auch entscheidend, ob die alternative Therapieform auch wahr- und angenommen wird, sei es bei Ärzten aber auch bei Nichtmedizinern. Zur Wahrnehmung und Akzeptanz der konservativen, antibiotischen Therapie der Appendizitis ist sehr wenig bekannt. Ich habe aus diesem Grund zum einen analysiert, wie diese Therapieform in sozialen Medien von verschiedenen Personen- bzw. Interessensgruppen widergespiegelt wird. Darüber hinaus habe ich die Akzeptanz, Anwendung und Einschätzung dieser Therapieoption bei in Deutschland klinisch tätigen Chirurgen abgefragt.

Die akute Appendizitis ist eine hochinteressante Erkrankung, bei der sich in allen Bereichen Veränderungen beobachten lassen: Diagnostisch gewinnen Scoring-Systeme und radiologische Verfahren zunehmend an Bedeutung. Therapeutisch erfolgte in den 1990er Jahren die Etablierung minimalinvasiver Techniken. Diese entwickelten sich bis heute zum Goldstandard. Auf die nichtoperativen Therapieansätze wurde bereits hingewiesen. Aber auch die Patienten mit akuter Appendizitis haben sich über die Jahre verändert. Lange Zeit war die Appendizitis eine Erkrankung des Kindesalters und von jungen Erwachsenen [39]. Vor dem Hintergrund alternder Gesellschaften, insbesondere in den entwickelten Ländern, rückt die Appendizitis des älteren Menschen zunehmend in den Fokus. Zum einen gibt es mehr ältere Patienten, zum anderen zeigte sich, dass auch bei über 50-Jährigen die Appendizitis häufig ist: die Appendizitis ist für bis zu 14 % der notfallmäßigen Vorstellungen aufgrund abdomineller Beschwerden in diesem Patientenkollektiv ursächlich [40]. Die endgültige Bedeutung der Appendizitis für ältere Menschen erschließt sich jedoch aus dem deutlich schlechteren Outcome dieser Patienten [41]. Verschiedene chirurgische Fachgesellschaften haben deshalb inzwischen Leitlinien verfasst, die speziell auf ältere Menschen ausgerichtet sind [42, 43].

Die geriatrische Forschung zeigt, dass die besonderen Herausforderungen und Risiken bei der Behandlung älterer Menschen nur bedingt mit dem nominalen Alter assoziiert sind. Die unkonkrete und wenig greifbare Formulierung “biologisches Alter” wurde in den letzten Jahren durch den Begriff “Gebrechlichkeit - Frailty” ersetzt, mit dem diese Risiken besser erfasst und beschrieben werden sollen. Mittlerweile gibt es für viele chirurgische Erkrankungen klare Daten, dass Gebrechlichkeit ein entscheidender Risikofaktor für ein ungünstiges Outcome ist [44]. Mein Ziel war es, dies auch für die Appendizitis des älteren Menschen zu untersuchen.

2. Ergebnisse und Diskussion der eigenen Arbeiten

2.1. Meteorologische Einflüsse auf die saisonalen Unterschiede im Krankheitsverlauf der akuten Appendizitis [45]

Umwelteinflüsse haben Einfluss auf das Auftreten und den Verlauf verschiedener Erkrankungen. Das Spektrum dieser Einflüsse reicht von klaren, bis auf zelluläre Ebene verstandenen Interaktionen zwischen Umwelteinfluss und Erkrankung bis hin zu reinen Assoziationen und vagen Beobachtungen. Beispielhaft für gut verstandene Zusammenhänge sind durch Lärmexposition ausgelöste bzw. aggravierte kardiovaskulären Erkrankungen, weniger klar verstanden sind die beobachteten Assoziationen zwischen Umweltverschmutzung und Adipositas [46, 47]. Ein Umweltfaktor, dem alle Menschen ausgesetzt und für welchen multiple Zusammenhänge zu akuten und chronischen Erkrankungen bekannt sind, ist das Wetter. Wir kennen Einflüsse des Wetters auf respiratorische und kardiovaskuläre Erkrankungen, aber auch auf abdominelle Erkrankungen wie die Cholezystitis, die Sigmadivertikulitis und die akute Appendizitis [48]. Betrachtet man die Inzidenz der Appendizitis, fallen Schwankungen über den Jahresverlauf mit einem Höhepunkt im Sommer auf [49]. Es liegt somit nahe, zu untersuchen, ob dies in Zusammenhang mit meteorologischen Faktoren steht. Wir haben hierzu an der Klinik für Allgemein-, Viszeral- und Transplantationschirurgie der Goethe-Universität Frankfurt am Main retrospektiv 688 Appendektomien der Jahre 2008 bis 2015 analysiert [45]. Über den Deutschen Wetterdienst Offenbach wurden die tagesaktuellen Wetterdaten für den Großraum Frankfurt am Main zur Verfügung gestellt. Zunächst erfolgte die rein kalendarische Analyse der Appendektomien: Wir konnten die Ergebnisse anderer Arbeitsgruppen zu saisonalen Inzidenzunterschieden der Appendizitis, wahrscheinlich aufgrund der geringen Stichprobengröße, nicht nachvollziehen. Interessanterweise zeigten sich jedoch signifikante Häufungen komplizierter, d. h. perforierter oder gangränöser Appendizitiden im Sommer und Winter. Ebenso beobachteten wir signifikant mehr komplikative postoperative Verläufe. Basierend auf dieser Beobachtung stellten wir die Hypothese auf, dass ein Zusammenhang zwischen meteorologischen Besonderheiten und komplizierten Appendizitiden sowie schweren postoperativen Verläufen besteht. Klare Korrelationen zwischen klinischen Parametern und einzelnen Wetterphänomenen oder den absoluten Werten der analysierten Faktoren Temperatur, Niederschläge, Luftfeuchtigkeit, Luftdruck und Bedeckungsgrad konnten nicht nachgewiesen werden. Daraufhin betrachteten wir die Tage mit *besonderem* Wetter, an denen sich die meteorologischen Messwerte stark von den üblichen Mittelwerten unterschieden (definiert als +/- eine Standardabweichung). Zudem wurden Tage untersucht, an welchen besondere Wettersituationen entsprechend meteorologischen Definitionen vorlagen, sogenannte „klimatologische Kenntage“ [50]. Auf diese Weise konnten wir Tage definieren, an denen Wetterumstände vorherrschten, die deutliche Unterschiede zu durchschnittlichen Tagen aufwiesen. Die weitere Analyse zeigte, dass nun klare Korrelationen zwischen Tagen mit besonders hohen oder niedrigen Temperaturen und dem Auftreten von komplizierten Appendizitiden feststellbar waren (**Abb. 1a**). Die multivariate Analyse ergab, dass Tage mit ungewöhnlich hohen oder niedrigen Temperaturen einen unabhängigen Risikofaktor für eine komplizierte Appendizitis darstellen. Dies spiegelte sich in der klinischen Versorgung wider: Wir konnten zeigen, dass nach Tagen mit ungewöhnlich hohen oder niedrigen Temperaturen signifikant mehr Patienten eine Peritonitis zum OP-Zeitpunkt hatten und signifikant mehr abdominelle Drainagen eingelegt wurden.

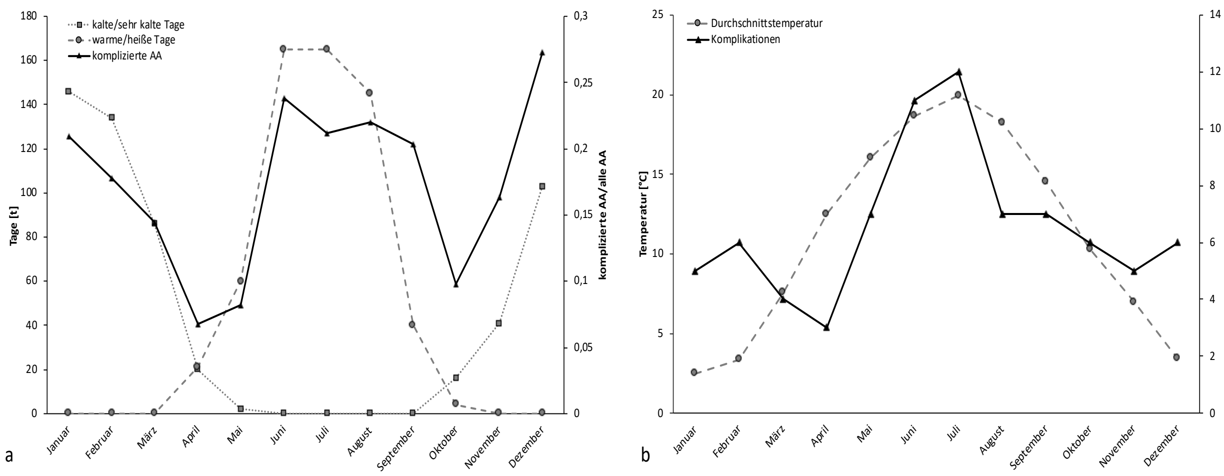

Abb. 1 Korrelation zwischen Wettersituationen und dem Auftreten von (a) komplizierten akuten Appendizitiden (AA) und (b) dem Auftreten von Komplikationen

Ein etwas anderes Bild fand sich bei der Betrachtung der postoperativen Verläufe: Bei der Analyse der Komplikationen nach Appendektomien beobachteten wir eine deutliche Häufung in den Sommermonaten. Die in unserer Kohorte häufigste Komplikation nach Appendektomie war die oberflächige oder tiefe Wundinfektion (Surgical Site Infection, SSI), sie machte 89 % aller Komplikationen aus. Bei Patienten, die nach besonders warmen oder gar heißen Tagen appendektomiert wurden, beobachteten wir signifikant mehr postoperative Komplikationen **(Abb. 1b).** Der größte Anstieg ließ sich bei Patienten, welche nach besonders warmen Tagen mit zudem besonders geringer Luftfeuchtigkeit operiert wurden, nachweisen (20,3 % Komplikationsrate vs. 11,1 % Komplikationsrate). Zudem beobachteten wir einen längeren postoperativen Aufenthalt nach warmen Tagen, wobei dieser Unterschied keine Signifikanz erreichte.

Auch wenn wir die aus großen Datenbankanalysen bekannten saisonalen Unterschiede im Auftreten der Appendizitis wohl aufgrund der Größe unserer Stichprobe nicht nachweisen konnten, ist es uns dennoch erstmals gelungen, klare Zusammenhänge zwischen meteorologischen Konditionen und sowohl dem Krankheitsverlauf (komplizierte vs. unkomplizierte Appendizitis) als auch für den postoperativen Verlauf nachzuweisen. Die erste Beobachtung liefert einen starken Hinweis darauf, dass Wetterbedingungen den Krankheitsverlauf beeinflussen, wobei die kausale Erklärung rein hypothetisch bleibt. Da die Höhepunkte sowohl in der warmen als auch in der kalten Jahreszeit, jedoch assoziiert mit außergewöhnlichen Temperaturen, auftreten, kann vermutet werden, dass diese besonders warmen oder besonders kalten Tage zu Änderungen im menschlichen Organismus führen. Mögliche Ansatzpunkte solcher Alterationen wären das Immunsystem oder das intestinale Mikrobiom, dies könnte wiederum die Entwicklung einer komplizierten Appendizitis begünstigen.

Die Beobachtung vermehrter komplikativer Verläufe nach besonders warmen Tagen kann nicht allein einer erhöhten Rate an komplizierten Appendizitiden geschuldet sein, da ein entsprechender Peak in den Wintermonaten völlig fehlt. Eine mögliche Erklärung hierfür ist, dass warme Temperaturen zu einer Alteration der Hautflora führen, was wiederum die SSIs begünstigt. Dies wurde bereits von anderen Arbeitsgruppen postuliert, unsere Studie war jedoch nicht darauf angelegt, hier tiefergehende Untersuchungen durchzuführen [51].

2.2. Mikrobiologische Analysen und deren klinische Implikationen bei akuter Appendizitis mit Peritonitis [21]

In der Einleitung ist die wahrscheinlich bedeutsame, wenn auch nur in Teilen verstandene Rolle von Bakterien für die Pathogenese und den Verlauf der akuten Appendizitis angesprochen worden. In dem Zeitraum, in dem sich eine akute Appendizitis entwickelt, haben wir klinischen Forscher nur sehr eingeschränkte Möglichkeiten das Mikrobiom der Appendix zu untersuchen. Einen Zugang zu den Erregern erhalten wir erst zum Zeitpunkt der Operation. Der intraoperative Abstrich jedoch ermöglicht die Bearbeitung wesentlicher Fragen zur Häufigkeit des Nachweises von Bakterien und Pilzen, zum Spektrum der Erreger, Antibiotikaresistenzen und insbesondere den damit korrelierten Verläufen. Unter anderem ist dies vor dem Hintergrund der gegenwärtig viel diskutierten antibiotischen, nichtoperativen Therapie der Appendizitis oder den Beobachtungen hinsichtlich antibiotikaresistenter Bakterien von größtem Interesse.

Zur Untersuchung des Erregerspektrums und dessen Einfluss auf den Krankheitsverlauf haben wir retrospektiv eine Kohorte von 590 nicht selektionierten, konsekutiven Patienten untersucht, welche zwischen 2008 und 2014 in der chirurgischen Klinik am Universitätsklinikum der Goethe-Universität Frankfurt aufgrund einer akuten Appendizitis operiert wurden. Die dabei gewonnenen Informationen über das Erregerspektrum in der beim Gesunden sterilen Peritonealhöhle in Umgebung der Appendix haben wir zudem mit den Keimnachweisen verglichen, welche wir bei Patienten mit nicht durch eine Appendizitis verursachten primären oder sekundären Peritonitiden im selben Untersuchungszeitraum isoliert hatten. Etwa 99 % der Patienten erhielten eine perioperative Antibiotikaprophylaxe. 38 % darüber hinaus eine perioperativ begonnene und postoperativ weiter durchgeführte Antibiotikatherapie mit zum damaligen Zeitpunkt für diese Indikation empfohlenen Antibiotika [52]. Abstriche bei Appendektomien wurden dann gewonnen, wenn bei der Operation trübe abdominelle Flüssigkeit, ein Abszess oder eine Perforation vorhanden war.

In ca. 60 % der entnommenen Abstriche konnten Bakterien, jeweils maximal drei verschiedene Spezies, nachgewiesen werden, in sechs Abstrichen Pilze. Häufigster nachgewiesener Erreger war E. coli (45 % der Abstriche), gefolgt von Bacteriodes spp. (20,5 %). Bei komplizierter, d. h. gangränöser oder perforierter Appendix (17 % der

Fälle), war der Anteil an positiven Abstrichen signifikant höher. Zudem konnten signifikant mehr verschiedene Erreger nachgewiesen werden.
Die Rate an Erregern mit, häufig multiplen, Antibiotikaresistenzen lag mit ca. 9 % der Isolate in einem Bereich, welcher für abdominelle Infektionen in Deutschland relativ niedrig war. All diese resistenten Keime ließen sich in die Gruppe der sogenannten ESKAPE-Bakterien einordnen: Enterobacteriacae, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumanii, Pseudomonas aeruginosa und Enterokokken [53]. Wir konnten eine deutliche Korrelation zwischen dem Nachweis dieser Bakterien und einem ungünstigen postoperativen Verlauf feststellen: Der Nachweis von Bakterien der ESKAPE-Gruppe war mit signifikant erhöhten Raten an infektiösen Komplikationen, einschließlich schwerwiegenden Wundinfektionen SSI Grad III korreliert. Wurden bei einer Appendektomie Bakterien isoliert, war dies mit einer signifikant längeren postoperativen Liegedauer verbunden. Waren es Erreger der ESKAPE-Gruppe, beobachteten wir eine zusätzliche, signifikante Verlängerung des Krankenhausaufenthaltes. Das nachgewiesene Spektrum bakterieller Erreger bei Appendizitis-Patienten unterschied sich vom Erregerspektrum bei Patienten mit primärer bzw. sekundärer, nicht durch eine Appendizitis verursachter, Peritonitis: Während Pseudomonas aeruginosa und Klebsiella pneumoniae ähnlich oft nachgewiesen wurden, fand sich ein signifikant geringerer Anteil an E. coli, jedoch ein Vielfaches an Enterokokken, einschließlich solcher mit Vancomycin Resistenz (VRE). Der Anteil mehrfachresistenter Bakterien war signifikant höher als bei der Appendizitis, zudem wurden signifikant mehr Pilze nachgewiesen.
Es war uns somit gelungen, die lokale infektiologische Situation bei akuter Appendizitis in einer nicht selektionierten Kohorte umfassend zu analysieren und klinische Korrelationen aufzuzeigen. Wir konnten nachweisen, dass sich das Erregerspektrum bei der akuten Appendizitis deutlich von dem bei anderen Peritonitisformen unterscheidet. Der Anteil an Erreger mit relevanten Antibiotikaresistenzen war nicht beunruhigend hoch, jedoch war ihr Nachweis mit einem ungünstigen klinischen Verlauf korreliert. Die Sinnhaftigkeit des Asservierens von Abstrichen bei Appendizitis wird von manchen Arbeitsgruppen in Frage gestellt [54, 55]. Dem kann anhand unserer Daten klar widersprochen werden. Weitere Auswertungen zeigten, dass das Ergebnis des Antibiogramms im Mittel nach 3,6 Tagen vorlag. Patienten mit komplikativen Verläufen waren im Mittel 5,2 Tage postoperativ stationär, Erregernachweis und Antibiogramm führten hier durchaus zu einer Beeinflussung der Therapie. Darüber hinaus wiesen wir,

zumindest für den damaligen Studienzeitraum, nach, dass die empfohlenen Antibiotika zur perioperativen Prophylaxe sowie zur Therapie angesichts der nachgewiesenen Keime und Resistenzen mit guter Erfolgsaussicht eingesetzt werden konnten.

2.3. Die Rezeption der konservativen Therapie der akuten Appendizitis in der medizinischen und nichtmedizinischen Öffentlichkeit am Beispiel sozialer Medien [56]

Es besteht seit jeher eine Dysbalance bezüglich der Zugänglichkeit zu medizinischen Fachinformationen zwischen medizinischen Laien und solchen, welche eine medizinische Ausbildung genossen haben oder im Gesundheitsbereich tätig sind. Dieses Ungleichgewicht verschiebt sich langsam, insbesondere angestoßen durch mündige Patienten und das Internet, zugunsten von Laien bzw. Patienten. Dennoch bestehen weiterhin gravierende Unterschiede bezüglich der Zugänglichkeit und Verfügbarkeit medizinischer Fachinformationen zwischen Medizinern und Nichtmedizinern. So sind spezialisierte medizinische Informationen, insbesondere Artikel aus medizinischen Fachzeitschriften oder Beiträge auf medizinischen Tagungen für Laien kaum verfügbar, zum Teil mit nicht unerheblichen Kosten verbunden und häufig schwer verständlich. Die nichtmedizinische Presse, das Fernsehen und insbesondere in den letzten Jahren die sozialen Medien füllen diese Informationslücke. Die wichtigste Rolle hierbei spielt Twitter®, eine Plattform, welche seit 2006 besteht und es dem Nutzer ermöglicht, sogenannte Mikroblogs („tweets“) zu veröffentlichen. Eine kritische Prüfung dieser erfolgt, abgesehen bei schwerwiegenden Straftaten und Urheberrechtsverletzungen, nicht. Im Bereich der Politik und Wirtschaft hat Twitter® in der westlichen Welt den größten Einfluss und Verbreitung, weit vor anderen sozialen Medien, aber auch im Gesundheitsbereich stellt es die wichtigste Informationsplattform dar [57]. Twitter® wird sowohl von medizinischen Laien wie auch Fachkräften sowie insbesondere von Organisationen bzw. Unternehmen genutzt. All diese Gruppen haben unterschiedliche Interessen bei der Publikation ihrer Mikroblogs. Die Tweets werden auch im medizinischen Bereich nicht auf ihre Richtigkeit, sei es in Form oder Inhalt, geprüft. Auch wenn sich die medizinische Wissenschaft zunehmend mit sozialen Medien beschäftigt, steht die Forschung hierzu noch am Anfang.

Unser Ziel war es, die Rolle von Twitter® im öffentlichen, internetbasierten Diskurs über die antibiotische, nichtoperative Therapie der akuten Appendizitis zu untersuchen. Eine häufige und auch unter medizinischen Laien gut bekannte

Erkrankung in Verbindung mit einer vermeintlich neuen, nichtoperativen Therapieform stellte hierfür einen optimalen Studiengegenstand dar. In einem mehrstufigen Suchprozess identifizierten wir zwischen 2011 und 2017 aus ca. 23.000 Tweets zur Appendizitis 364 Tweets, welche sich ernsthaft mit der antibiotischen Therapie der akuten Appendizitis beschäftigten. Es fiel zunächst auf, dass aus einer Tweet-Grundfrequenz in bestimmten Monaten Spitzen mit plötzlicher Vervielfachung der relevanten Tweets auftraten. Diese setzten wir in Verbindung zu Publikationen in medizinischen Fachzeitschriften. Es gelang uns zu demonstrieren, dass diese Maxima auf die Veröffentlichung wichtiger Studien zur antibiotischen Therapie der akuten Appendizitis in den wichtigsten medizinischen Fachzeitschriften folgten.

Die Betrachtung der Urheber der Tweets zeigte, dass diese in ähnlichem Verhältnis von Individualpersonen und von Organisationen veröffentlicht wurden. Bei den Individualpersonen bezeichnete sich die größte Gruppe als medizinische Fachkräfte (68 % Ärzte, davon 35 % Chirurgen). Bei den Organisationen stammten die meisten Tweets von professionellen Publikationsplattformen wie z. B. Medienhäuser (65 %), gefolgt von Unternehmen bzw. Nichtregierungsorganisationen und Krankenhäusern bzw. Regierungsorganisationen.

Da Tweets weitgehend ungeprüft veröffentlicht werden, war auch die Inhaltsanalyse entscheidend. Hierbei fokussierten wir uns darauf zu prüfen, wie die antibiotische Therapie der akuten Appendizitis dargestellt wird. In der wissenschaftlichen Diskussion ist eine abschließende Beurteilung dieser Therapieform noch nicht erfolgt. Die Effektivität sowie Vor- und Nachteile werden lebhaft diskutiert. Einen Tweet, welcher dies widerspiegelte, klassifizierten wir als „neutral“. Hiervon unterschieden wir Tweets, welche die antibiotische Therapie positiv oder negativ darstellten und unterteilten weiter in solche, welche diese Wertung differenziert unter Betonung der Vor- oder Nachteile vornahmen (positiv/negativ) und solche, welche vollkommen unkritisch eine eindeutige Wertung abgaben (inadäquat positiv/negativ). In der Gesamtkohorte ließ sich, bei überwiegend neutraler Darstellung, eine Tendenz zu einer positiven Darstellung der konservativen Therapie der Appendizitis feststellen. Interessanterweise fanden sich signifikante Unterschiede in der wertenden Darstellung in den verschiedenen Urhebergruppen: Chirurgen publizierten neutrale bis hin zu kritischen Tweets, bei den medizinischen Laien und den Allgemeinmediziner dominierten klar die Tweets, welche die antibiotische Therapie der akuten Appendizitis positiv bis hin zu inadäquat positiv darstellten (**Tab. 1**). Organisationelle Tweets waren überwiegend neutral, jedoch ebenfalls mit einer Tendenz zur positiven Darstellung.

Tab. 1 Wertende Darstellung der nichtoperativen, antibiotischen Therapie der akuten Appendizitis durch verschiedene Verfassergruppen von Tweets

		inadäquat positiv		positiv		neutral		negativ		inadäquat negativ	
Individuen (IND)	medizinische Laien	25.86		41.38		29.31		3.45		0.0	
		4.3	8.98	6.88	14.37	4.87	10.18	0.57	1.2	0.0	0.0
	Allgemeinmediziner	22.22		44.44		11.11		11.11		11.11	
		0.57	1.2	1.15	2.4	0.29	0.6	0.29	0.6	0.29	0.6
	sonstige medizinische Fachkräfte	7.69		34.62		50		7.69		0.0	
		0.57	1.2	2,58	5.39	3.72	7.78	0.57	1.2	0.0	0.0
	Fachärzte (außer Chirurgen)	4.17		41.67		43.75		10.42		0.0	
		0.57	1.2	5.73	11.98	6.02	12.57	1.43	2.99	0.0	0.0
	Chirurgen	7.69		7.69		50		34.62		0.0	
		0.57	1.2	0.57	1.2	3.72	7.78	2,58	5.39	0.0	0.0
	IND	6.59	13.77	16.91	35.33	18.62	38.92	5,44	11,4	0.29	0.6
Organisationen (ORG)	Firmen, Nicht-Regierungsorganisationen	18.18		27.27		45.45		9.09		0.0	
		1.72	3.3	2.58	4.95	4.3	8.24	0.86	1.65	0.0	0.0
	Krankenhäuser, Öffentliche- und Regierungsorganisationen	3.23		22.58		67.74		6.45		0.0	
		0.29	0.55	2.01	3.85	6.02	11.54	0.57	1.1	0.0	0.0
	Nachrichtenagenturen, Publikationsplattformen	9.32		22.88		65.25		2.54		0.0	
		3.15	6.04	7.74	14.84	22.06	42.31	0.86	1.65	0.0	0.0
	ORG	5.16	9.89	12.32	23.63	32.38	62.09	2.29	4.4	0.0	0.0

Legende	[%] der Gruppe	
	[%] aller	[%] von IND/ORG

0-9.9	10-19.9	20-29.9	30-39.9	40-49.9	50-59.9	60-69.9

Die Leserzahl medizinischer Fachzeitschriften ist begrenzt. Nach Angaben der Verlage werden selbst Manuskripte in renommierten Zeitschriften durchschnittlich wenige tausend Mal heruntergeladen [58]. Verglichen hiermit ist der numerische Impact der untersuchten Tweets sehr groß: Im Mittel hatten die Urheber weit über 10.000, im Maximum bis 393.000 Leser („follower“). Hierbei hatten Organisationen signifikant mehr follower, was zu einer Verzerrung führte: Individuelle Urheber von Tweets hatten im Mittel nur 1468 +/- 345 follower. Bei nur einem Teil der Tweets konnten wir eindeutig erkennen, dass diese wahrgenommen wurden: sie wurden weitergeleitet („re-tweeted“) beziehungsweise als lesenswert markiert („like“). Auch unter den beiden letztgenannten Parametern fanden sich signifikant mehr positive Tweets, verglichen mit der neutralen Darstellung.

Unsere Arbeit zählt zu den ersten, welche die Rolle von sozialen Medien für die Verbreitung von Informationen zu Gesundheitsthemen, speziell im Bereich der Chirurgie, untersuchte. Sie zeigte zum einen, dass die fachliche Diskussion über eine alternative Therapieform wie die antibiotische Therapie der akuten Appendizitis von Twitter®-Nutzern wahrgenommen und reflektiert wird. Es gelang uns nachzuweisen, dass das Mikroblogging durch die medizinische Fachpresse getriggert wird, zumindest bei hohem Impact und einer für die allgemeine Öffentlichkeit interessanten Erkrankung. Die Publikation der Tweets erfolgt ungeprüft und, entsprechend dem Konzept des Mikroblogs, stark verkürzt. Wir beobachteten kritisch eine überwiegend positive Darstellung der alternativen Therapieform. Allerdings besteht auch bei den klassischen, wissenschaftlichen Publikationen ein positiver Publikationsbias, dem diese Beobachtung vielleicht in Teilen entspricht [59].

2.4. Die Anwendung und Bewertung der antibiotischen, nichtoperativen Therapie der akuten Appendizitis durch Chirurgen in Deutschland [60]

Die rege Diskussion eines alternativen Therapieansatzes wie der antibiotischen, nichtoperativen Therapie der akuten Appendizitis im Erwachsenenalter in der wissenschaftlichen Community und der nichtmedizinischen Öffentlichkeit erlaubt keine Einschätzung, ob und in welchem Umfang diese Therapieform in der klinischen Praxis Anwendung findet. In einer Studie aus dem Jahr 2018 wurde für die USA eine Rate von konservativ behandelten Appendizitiden von 14 % angegeben [61]. Daten aus Deutschland gab es bislang nicht. Wir führten deshalb eine Umfrage unter klinisch tätigen Chirurgen in allgemein- und viszeralchirurgischen Kliniken durch. Entsprechend des Anteils an der Versorgung von Patienten mit Appendizitis, differenziert nach Bundesländern und unter gesonderte Betrachtung der fünf großen Metropolenregionen Deutschlands wurden 1400 Chirurgen, deren E-Mail-Adresse öffentlich zugängig war, angeschrieben. Die Auswahl der Ärzte erfolgte zufällig aus einer Datenbank von über 2700 Kliniken, jedoch nach einem festgelegten Schlüssel zum Versorgungsgrad der Krankenhäuser. Wir erfragten, ob und unter welchen Bedingungen eine konservative, antibiotische Therapie der akuten Appendizitis bei erwachsenen Patienten durchgeführt wird, wie hoch der Anteil an konservativen Behandlungen ist und aus welchen Gründen diese abgelehnt wird. Um darüber hinaus einen Eindruck zur Einstellung der Kollegen zu dieser Behandlungsform zu bekommen, fragten wir, ob die Chirurgen sich selbst oder Angehörige bzw. Freunde konservativ behandeln würden und erfassten außerdem deren Erwartungen an diese Therapieform für die Zukunft.

Wir erreichten mit 19,9 % eine akzeptable Rücklaufquote, diese lag signifikant höher bei Ärzten von Maximalversorgern und Universitätskliniken. 14 % aller Chirurgen gaben an, dass die konservative Therapie der Appendizitis von ihnen regelmäßig durchgeführt wird, wobei sich zeigte, dass auch diese nur den kleinsten Teil ihrer Patienten (61,5 % weniger als 10 % der Patienten mit Appendizitis) konservativ behandeln. 38,1 % der Chirurgen behandeln in *Ausnahmefällen/besonderen Fällen* Appendizitiden konservativ, 48,8 % lehnen diese Therapieoption ab. Für eine konservative Therapie wird von fast allen eine Bildgebung, zumeist Sonographie gefolgt von Computertomographie oder Kernspintomographie gefordert, ebenso gehören die Leukozyten und das CRP zu den Parametern, die von 92,3 % der Behandler gewünscht werden. Für 89,7 % der Chirurgen war der klinische Gesamteindruck der entscheidende Parameter, ob sie ihre Patienten einem konservativen Therapieversuch zuführen.

Bei Chirurgen, welche die konservative Therapie regelmäßig durchführen, geht die Initiative hierzu in einem Drittel der Fälle vom Behandler und einem Fünftel vom Patienten aus, in etwa der Hälfte der Fälle war es eine gemeinsame Entscheidung. Die Zufriedenheit mit der nichtoperativen, antibiotischen Behandlung ist hoch: 79,5 % der Behandler waren *zufrieden* oder *sehr zufrieden*, keiner unzufrieden. Diejenigen, welche eine konservative Therapie der Appendizitis regelhaft durchführen, bewerten die negativen Konsequenzen einer Appendektomie als signifikant schwerwiegender als solche, die diese Therapieoption nicht oder nur in Ausnahmefällen durchführen (**Abb. 2a**).

Die größte Gruppe an Chirurgen sehen die konservative Therapie der Appendizitis nur in *Ausnahmefällen/besonderen Fällen* als indiziert an. Hierbei ist der explizite, aktive Wunsch des Patienten der häufigste Grund (40,9 %), gefolgt von einer sehr milden Klinik (19,1 %) und sehr hohem perioperativen Risiko (18,2 %). Auf die Frage, warum Ärzte die konservative Therapie nicht regelhaft anwenden, geben diese an, Zweifel an ihrer Effektivität zu haben (51 %). Sie betrachten die Evidenzlage als nicht eindeutig oder haben Bedenken hinsichtlich rechtlicher Konsequenzen (je 39 %). Monetäre Aspekte spielen eine nachrangige Rolle. Die gleichen Argumente werden auch in der Gruppe der Behandler genannt, welche die konservative Therapie ablehnen. Auffallend ist, dass Ärzte, welche die konservative Therapie ablehnen, signifikant häufiger an Krankenhäusern der Grund-, Regel- und Schwerpunktversorgung tätig sind.

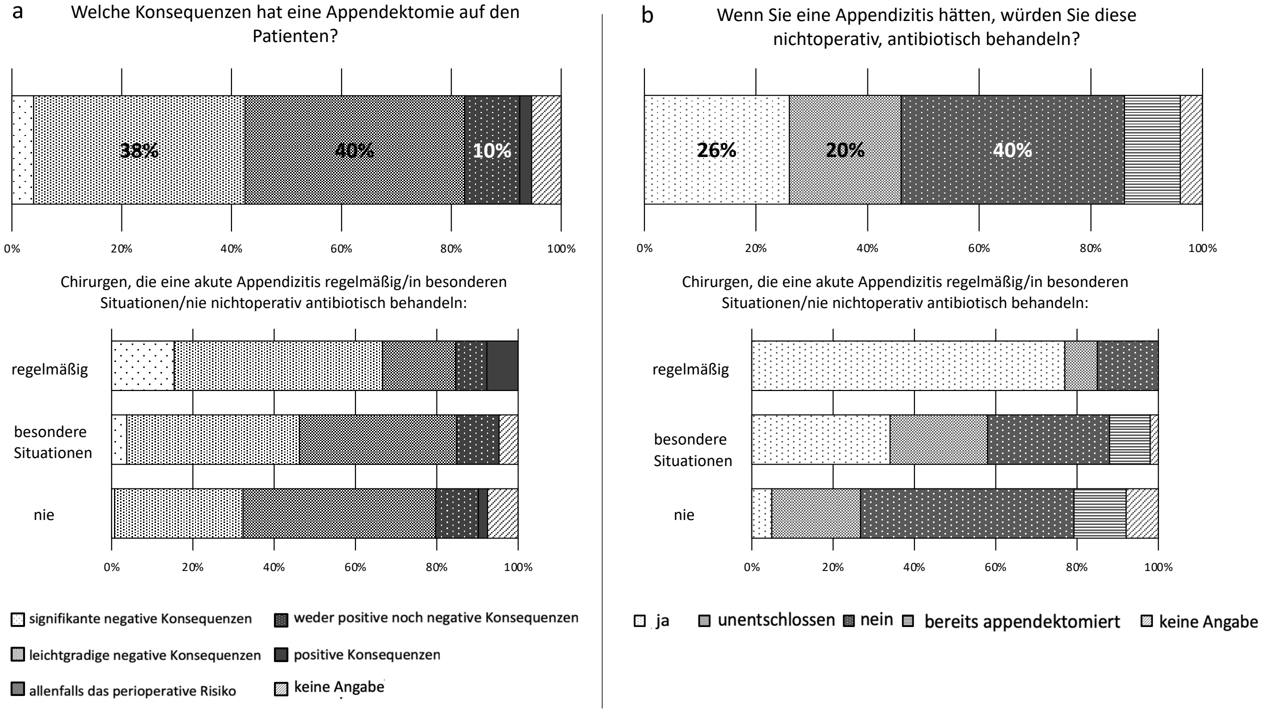

Abb. 2 Einschätzungen und Erwartungen bezüglich der nichtoperativen, antibiotischen Therapie der akuten Appendizitis bei Behandlern, die diese Therapie regelmäßig, in besonderen Situationen oder nie anwenden.

Ob ein Chirurg eine Appendizitis konservativ behandelt, scheint, neben den o. g. Bedenken gegenüber dieser Therapie auch Ausdruck einer generellen Einstellung zu dieser Therapieform zu sein: Gefragt nach einer hypothetischen Behandlung von Angehörigen oder Freunden und der Behandlung, die man bei sich selbst anwenden würde, ergibt sich ein dichotomes Bild: 40% aller Befragten würden eine nichtoperative Therapie für sich selbst ablehnen. Es zeigen sich hierbei jedoch signifikante Unterschiede zwischen den Untergruppen: Diejenigen, welche die unkomplizierte Appendizitis regelhaft konservativ behandeln, würden dies zu fast 77 % auch bei sich selbst versuchen; solche, die nie konservativ behandeln, zu weniger als 5 %. Hinsichtlich der Behandlung von Angehörigen und Freunden verschiebt sich das Spektrum leicht zu Ungunsten der konservativen Therapie (**Abb.2b**).

Die Erwartungen an die zukünftige Entwicklung und Bedeutung der nichtoperativen Therapie der akuten Appendizitis ist heterogen. In der Gesamtkohorte rechnet ein Drittel mit einer zunehmenden, ein Drittel nicht mit einer zunehmenden Bedeutung der konservativen Therapie. Das letzte Drittel ist unentschlossen. Diese Erwartungen basieren nur teilweise auf der aktuellen Evidenzlage, allenfalls ein Teil der

unentschlossenen Chirurgen würde (häufiger) konservativ behandeln, sollte sich die Evidenzlage zugunsten der nicht operativen Therapie verbessern.
Die demographische Auswertung bestätigt die bereits teilweise aufgeführten Unterschiede zwischen Chirurgen aus städtischen und ländlichen Regionen, hinsichtlich der Tätigkeitsstelle und zum Teil der Berufserfahrung. Unterschiede zwischen den Bundesländern waren nicht zu beobachten. Es finden sich jedoch Tendenzen und signifikante Unterschiede zugunsten der konservativen Therapie, sowohl bezüglich Anwendung als auch Einschätzung, in den fünf deutschen Metropolregionen, sowie bei Kollegen von Maximalversorgern und Universitätskrankenhäusern.
Unsere Ergebnisse demonstrieren somit erstmals für Deutschland, dass die nichtoperative, antibiotische Therapie der akuten Appendizitis zwar in der klinischen Praxis angewendet wird, jedoch mitnichten eine generelle Änderung der klinischen Praxis zu beobachten ist. Diese Therapieoption wird von einem Teil der Chirurgen regelhaft oder in besonderen Behandlungssituationen angewendet. Allerdings machen die so behandelten erwachsenen Patienten in unserer Befragung nur einen kleinen Anteil der Patienten mit akuter Appendizitis aus. Hinweise darauf, dass sich dies zukünftig deutlich ändern wird, konnten wir nicht finden.

2.5. Gebrechlichkeit als besonderer Risikofaktor bei älteren Menschen mit akuter Appendizitis [62]

Die Anzahl sowie der Anteil an älteren Menschen in Deutschland steigen seit vielen Jahren deutlich an. Im Jahre 2020 lebten in Deutschland ca. 18,3 Millionen Menschen mit einem Alter über 65 Jahre, davon 2,5 Millionen sogenannte Hochbetagte, d. h. Menschen über 85 Jahre [63]. Ältere Menschen stellen die größte Gruppe unter den stationär behandelten Patienten dar und sind dabei besonderen Risiken ausgesetzt [64]. Diese sind jedoch nicht unmittelbar durch das numerische Alter zu erklären. Vielmehr ist die individuelle Fitness bzw. deren negatives Korrelat, die Gebrechlichkeit (Frailty) ein entscheidender Parameter, um die Risiken einer medizinischen Behandlung für den älteren Menschen abzuschätzen.
Gebrechlichkeit ist ein multidimensionales Syndrom, bedingt durch eine insbesondere altersbedingte Dysregulation mehrerer physiologischer Regelkreise mit konsekutiv herabgesetzter Belastbarkeit und erhöhter Vulnerabilität [65, 66]. Eine einheitliche

Definition existiert nicht, zudem sind über 70 verschiedene Assessments zur Erfassung der Gebrechlichkeit beschrieben. Ohne dass eine klare Abgrenzung möglich ist, basieren die gängigen Konzepte von Gebrechlichkeit entweder auf dem Defizit-Akkumulations-Modell, beschrieben von Rockwood und Mitnitski [67] oder der Annahme eines physischen Gebrechlichkeits-Phänotyps („physical phenotyp of frailty“) nach Linda P. Fried [65]. Darüber hinaus existieren Kombinationen beider Modelle [66].

Wie einführend erwähnt, kann die akute Appendizitis nicht mehr als Erkrankung des jungen Erwachsenen angesehen werden. Die demographische Entwicklung führt dazu, dass die Appendizitis des älteren Menschen mit den damit verbundenen Besonderheiten inzwischen große Aufmerksamkeit erfährt. Unter jüngeren, nicht vorerkrankten Menschen sind die Morbidität und Mortalität der Appendizitis gering. Bei älteren Patienten hingegen lassen sich perioperative Komplikationsraten bis über 35 % sowie eine relevante Mortalität feststellen [68]. Vor diesem Hintergrund untersuchte ich, ob dieses auffallend schlechte Outcome in Zusammenhang mit Gebrechlichkeit steht. Für eine akute Erkrankung, wie die Appendizitis, besteht nicht die Möglichkeit, den präoperativen Zustand, beispielsweise durch *Pre*habilitation, zu verbessern. Allerdings gibt die frühe Identifikation von Patienten mit erhöhtem Risiko die Möglichkeit, dass sich die behandelnden Ärzte auf die damit verbundenen Herausforderungen bereits peri- und unmittelbar postoperativ einstellen.

Hierzu erfolgte die retrospektive Analyse aller aufgrund einer akuten Appendizitis von 2015 bis 2020 am Universitätsklinikum Gießen, Klinikum Wetzlar und den Dill-Kliniken Dillenburg operierten Patienten. Eingeschlossen wurden Patienten mit akuter Appendizitis, welche zum Operationszeitpunkt älter als 65 Jahre waren und bei welchen im dreimonatigen Zeitraum der Nachkontrolle keine elektive Wiederaufnahme oder geplante weitere Interventionen oder Operationen stattfanden. Wir wählten Frailty-Assessments, welche retrospektiv auf Basis der Patientenakte anwendbar waren und zugleich ohne spezielle Zusatzuntersuchungen durchgeführt werden konnten. Diese sollten in einem chirurgischen Krankengut validiert und auch durch nicht geriatrisch geschulte Ärzte anwendbar sein. Für die Analyse nutzten wir zum einen den komplexen, auf der DRG-Kodierung basierenden *Hospital Frailty Risk Score* (HFRS) nach Thomas Gilbert [69], zum anderen den deutlich kürzeren *modified Frailty Index* (mFI) von Vic Velanovich [70], letzterer eine Weiterentwicklung des vom Rockwood und Mitnitskis erarbeiteten Canadian Study of Health and Aging-frailty

Index [14]. Während ersterer über hundert Parameter erfasst, fragt der mFI in der klassischen Form nur elf Parameter ab (mFI-11). Zusätzlich untersuchten wir die vereinfachte, ebenfalls validierte Form des mFI mit nur fünf Parametern (mFI-5). Hauptziel der Studie war die Analyse von Korrelationen zwischen Gebrechlichkeit (gemessen mit den genannten Assessments) und negativem Outcome. Ergänzend zu typischen chirurgischen Outcomeparametern wie Intensiv- und Liegezeiten, Wiederaufnahmen, Morbidität und Mortalität erfassten wir zudem, ob es den Patienten postoperativ gelingt, wieder in das Umfeld zurückzukehren, in welchem sie vor der Appendizitis gelebt hatten. Nebenzielgrößen waren die Erfassungsqualität sowie der für die Assessments nötige Zeitaufwand.

In dem von uns untersuchten Kollektiv waren 10,2 % der Patienten über 65 Jahre alt. Von diesen wiederum gab es bei 18,2 % in den von uns durchgeführten Assessments keinen Hinweis für Gebrechlichkeit. Ließ sich Gebrechlichkeit nachweisen, war dies mit einem ungünstigen individuellen Outcome verbunden. Diese Patienten erlitten signifikant häufiger Komplikationen, sowohl leicht- als auch schwergradige. Sie benötigten häufiger postoperativ eine Behandlung auf der Intensivstation und hatten einen signifikant längeren Krankenhausaufenthalt. Die multivariate Analyse ergab, dass Gebrechlichkeit für die genannten Parameter ein eigenständiger, signifikanter Risikofaktor ist. Bei deutlichen Anzeichen von Gebrechlichkeit (HFRS >/= 5) lag die Odds-Ratio beispielsweise für schwerwiegende Komplikationen bei 4,9 (1,5 - 16,7; 95 % Konfidenzintervall (KI)), für die Notwendigkeit einer Intensivtherapie bei 5,2 (2,3 - 11,5; 95 % KI) oder bei 4,5 (1,5 - 13,3; 95 % KI) für das Risiko, nicht mehr in das bisherige Wohnumfeld zurückkehren zu können. Auch die Mortalität war bei gebrechlichen Patienten erhöht, wobei die geringe Anzahl verstorbener Patienten (n = 5) hier keine sinnvolle multivariate Analyse ermöglichte. Darüber hinaus gelang es uns zu zeigen, dass diese erfassten Risiken mit steigenden Werten in den Assessments, somit mit „zunehmender“ Gebrechlichkeit ansteigen, also kein rein dichotomer Zusammenhang besteht (**Abb. 3**). Die Korrelation zwischen Gebrechlichkeit und negativem Outcome, oben beispielhaft für einige Parameter und den HFRS aufgeführt, fanden sich analog beim mFI-11 und mFI-5. Hier waren nun die Nebenzielgrößen hochinteressant: Es zeigte sich, dass sich der mFI signifikant schneller als der HFRS erfassen lässt (21,6 Sek. (0 – 45 Sek.) vs. 80,3 Sek. (0 – 220 Sek.)). Zudem erwies sich die Erfassung des mFI als akkurater verglichen mit dem HFRS.

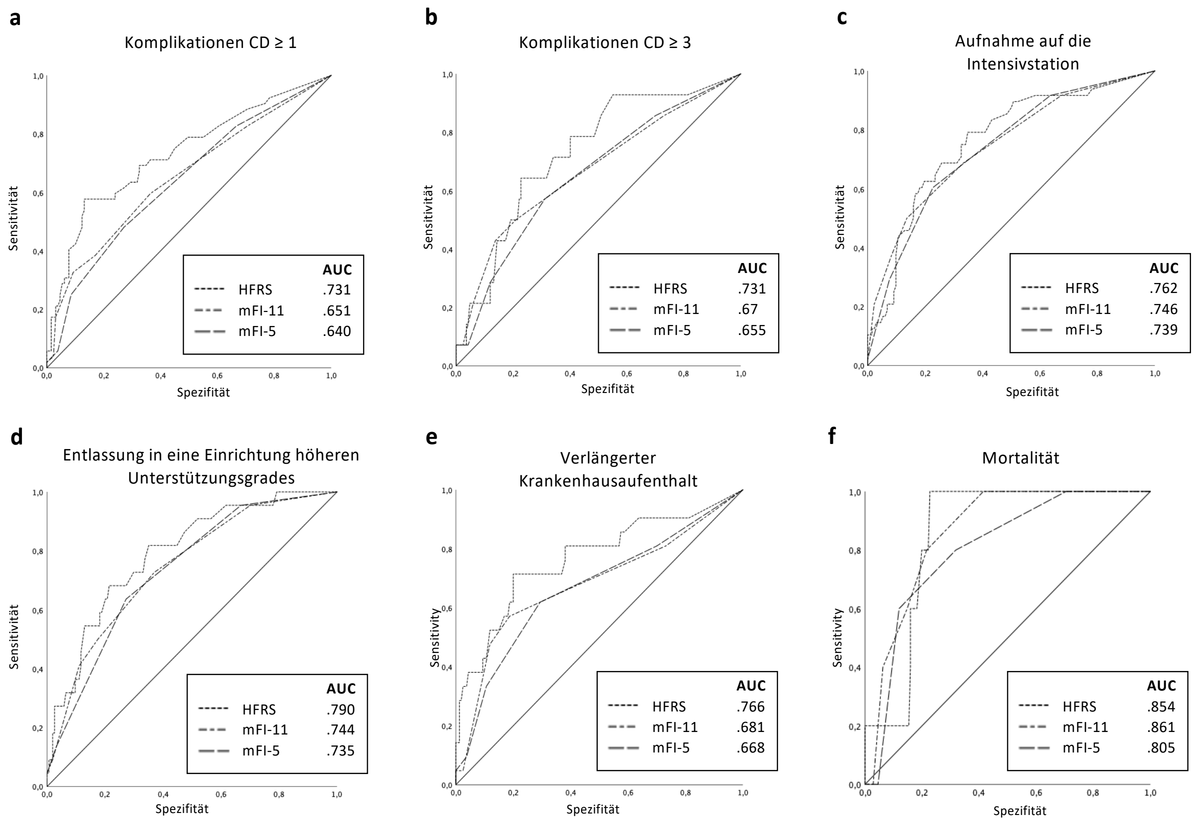

Abb.3 Receiver Operating Characteristic Kurven (ROC) des Hospital Frailty Risk Score (HFRS) und modified Frailty Index (mFI) 5 & 11 für **a** Komplikationen entsprechend der Clavien-Dindo Klassifikation (CD) ≥ 1; **b** CD ≥ 3; **c** Aufnahme auf die Intensivstation; **d** Entlassung in eine Einrichtung höheren Unterstützungsgrades verglichen mit dem vorstationären dauerhaften Aufenthalt; **e** Verlängerter Krankenhausaufenthalt = Mittlere Aufenthaltsdauer + 1 Standardabweichung; **f** Mortalität; AUC – Area under the curve

Wir konnten mit unserer multizentrischen Studie erstmals zeigen, dass Gebrechlichkeit ein unabhängiger Risikofaktor für ein ungünstiges Outcome bei älteren Patienten mit akuter Appendizitis ist. Bei akuten Erkrankungen besteht nicht die Möglichkeit, die Gebrechlichkeit der Patienten vor Behandlungsbeginn durch eine Prähabilitation zu bessern. Allerdings kann, werden entsprechende Betroffenen früh identifiziert, die Behandlung auf die speziellen Risiken angepasst werden: Beispiele hierfür wären der Verzicht auf Benzodiazepine bei der Narkose gebrechlicher Patienten, da dies mit häufig auftretendem postoperativem Delir und somit wiederum mit einer Behandlung auf der Intensivstation assoziiert ist. Weiterhin bestände die Möglichkeit, durch z. B. forcierte postoperative Physiotherapie oder zusätzliche Labor- oder Ultraschalluntersuchungen mögliche Komplikationen abzuwenden, früh zu erfassen und gezielt zu therapieren. Auch organisatorisch kann optimiert auf diese Menschen eingegangen werden, insbesondere durch die frühe Einbindung des Sozialdienstes. Uns gelang es nachzuweisen, dass gebrechliche, ältere Patienten sich mit einem einfachen Assessment identifizieren lassen. Diese können in unter einer Minute von nicht geriatrisch geschulten Ärzten durchgeführt werden, was eine breite klinische Anwendung ermöglicht.

3. Zusammenfassung

Diese kumulative Habilitationsschrift fasst meine Arbeiten zur akuten Appendizitis zusammen. Sie beleuchtet dabei ein breites Spektrum der aktuellen klinischen Forschung zu einer der häufigsten viszeralchirurgischen Erkrankungen. Es gelang mir einerseits durch meine Studien Faktoren zu identifizieren, über welche unmittelbar die klinische Versorgung der Patienten mit akuter Appendizitis verbessert werden kann. Andererseits konnte ich wichtige Einblicke in die Anwendung und Rezeption alternativer Therapieoptionen für diese Erkrankung gewinnen.

Einen Einfluss auf die klinische Versorgung von Patienten mit akuter Appendizitis haben unsere Analysen zum mikrobiellen Spektrum im Bereich der entzündeten Appendix vermiformis. Wir konnten zeigen, dass der Nachweis hochpathogener Bakterien, teilweise mit problematischen Resistenzen auf häufig eingesetzte Antibiotika, mit einem ungünstigen postoperativen Verlauf assoziiert ist. Dies liefert ein valides Argument für die systematische Entnahme von mikrobiologischen Proben bei Appendektomien, ein Vorgehen, welches nicht unumstritten war und ist. Lassen sich hierbei potenziell problematische Erreger nachweisen, ist eine engmaschige Überwachung bezüglich infektiologischer Komplikationen möglich. Beim Auftreten einer solchen Infektion kann dann eine antibiogrammgerechte Therapie begonnen werden.

Auch zu weiteren Faktoren, welche einen Einfluss auf den klinischen Verlauf von Patienten mit akuter Appendizitis haben, konnten wir wichtige Erkenntnisse gewinnen. So zeigte sich, dass besondere Wettersituationen mit schwereren Verläufen der Erkrankung assoziiert sind. In Zusammenhang mit Tagen, an welchen besonders hohe oder niedrige Temperaturen vorherrschten, traten häufiger komplizierte, d. h. gangränöse oder perforierte Appendizitiden auf. Zudem fand sich zum Operationszeitpunkt häufiger eine Peritonitis. In Zeiträumen mit besonders hohen Temperaturen traten vermehrt postoperative Komplikationen, insbesondere Wundinfektionen, auf. Gerade letztere Beobachtung sollte Anlass dazu geben, auch unter Würdigung der in unserer mikrobiologischen Studie gewonnenen Erkenntnisse, Patienten, die an oder nach Tagen mit besonderer Wettersituation operiert wurden, mit gesteigerter Aufmerksamkeit postoperativ zu betreuen.

Zwei meiner Arbeiten beschäftigten sich mit der nichtoperativen, antibiotischen Therapie der akuten Appendizitis. Hierbei lag unser Fokus nicht auf den unmittelbaren klinischen Aspekten dieser Therapieoption, sondern viel mehr auf deren Anwendung und Rezeption. Uns gelang es erstmalig, für Deutschland Informationen zur klinischen Verbreitung dieser Therapie zu erheben. Hierbei zeigte sich, dass die konservative, antibiotische Therapie von vielen Chirurgen durchgeführt wird, häufig jedoch nur bei einem sehr kleinen Anteil ihrer Patienten. Die antibiotische, nicht operative Therapie wird zu einem erheblichen Anteil nur in besonderen Konstellationen wie z. B. gering ausgeprägtem klinischen Befund oder hohem perioperativen Risiko angewendet. Die Befragung der Chirurgen ergab, dass diese die alternative Therapieform differenziert einschätzen. Es zeigt sich ein deutlicher Unterschied zu meiner zweiten Arbeit in diesem Themenkomplex. In den sozialen Medien, von uns am Beispiel Twitter® untersucht, wird die antibiotische, nichtoperative Therapie der Appendizitis tendenziös positiv dargestellt. Wir konnten zeigen, dass je nach Interessensgruppe zum Teil eine sehr zugespitzte und teilweise inadäquat positive oder negative Einschätzung dieser Therapie vorgenommen wird. Vor allem jedoch gelang uns der Nachweis, dass das Thema der Therapie der Appendizitis tatsächlich in sozialen Medien, auch über medizinische Fachkreise hinaus, lebhaft diskutiert wird. Wenn wir Patienten mit akuter Appendizitis behandeln, sollten wir wissen, wie alternative Therapieformen in der Fach- und Laienöffentlichkeit diskutiert werden und auch wie unsere Kollegen diese einschätzen. Gerade das macht den besonderen Wert dieser beiden Arbeiten aus.

In meiner fünften Arbeit im Themenkreis Appendizitis untersuchten wir vor dem Hintergrund einer alternden Gesellschaft und einer steigenden Anzahl an älteren Patienten mit Appendizitis den Einfluss von Gebrechlichkeit auf den Krankheitsverlauf. In dieser multizentrischen Analyse konnten wir klar nachweisen, dass Gebrechlichkeit, über das hohe Alter per se hinaus, einen entscheidenden, unabhängigen Risikofaktor für ein negatives Outcome nach Appendektomie darstellt. Gebrechliche Patienten erleiden beispielsweise häufiger postoperative Komplikationen. Auch das Risiko, aus dem Krankenhaus nicht mehr in das gewohnte Lebensumfeld zurückkehren zu können, ist signifikant erhöht. Durch den Vergleich verschiedener Assessment-Werkzeuge konnten wir demonstrieren, dass insbesondere der mFI die schnelle und sichere Identifikation von gebrechlichen Patienten erlaubt. Dies ermöglicht es, den besonderen Bedürfnissen dieser Patientengruppe, sei es medizinisch oder organisatorisch, Rechnung zu tragen.

Die hier zusammengefassten Arbeiten zeigen die großen Möglichkeiten klinischer Forschung an Patienten mit akuter Appendizitis. Unsere Ergebnisse tragen zu einer Therapieoptimierung bei den mehr als 100.000 in Deutschland jedes Jahr behandelten Patienten mit akuter Appendizitis bei.

4. Literaturverzeichnis

1. Malkomes P, Edmaier F, Liese J, Reinisch-Liese A, El Youzouri H, Schreckenbach T, et al. DIALAPP: a prospective validation of a new diagnostic algorithm for acute appendicitis. Langenbecks Arch Surg. 2021;406(1):141-152. doi: 10.1007/s00423-020-02022-7.

2. Saegesser M, Denecke H, Abendroth D. Saegesser - spezielle chirurgische Therapie. Bern: Verlag Hans Huber; 1996.

3. Sachs M. Geschichte der operativen Chirurgie. Heidelberg: Kaden; 2000.

4. Parkinson J. Case of diseased Appendix Vermiformis. Med Chir Trans. 1812;3:57-8.

5. Merling F. Diss. sistens processus vermiformis anatomiam pathologicam. Universtität Heidelberg; 1836.

6. Rockitansky C. A manual of pathological anatomy (1855, Übersetzung der Orginalpublikaiton, Wien 1842). Philadelphia: Blancard and Lea; 1842.

7. Lamps LW. Infectious causes of appendicitis. Infect Dis Clin North Am. 2010;24(4):995-1018, ix-x. doi: 10.1016/j.idc.2010.07.012.

8. Carr NJ. The pathology of acute appendicitis. Ann Diagn Pathol. 2000;4(1):46-58. doi: 10.1016/s1092-9134(00)90011-x.

9. Burkitt DP, Moolgaokar AS, Tovey FI. Aetiology of appendicitis. Br Med J. 1979;1(6163):620. doi: 10.1136/bmj.1.6163.620.

10. Bhangu A, Søreide K, Di Saverio S, Assarsson JH, Drake FT. Acute appendicitis: modern understanding of pathogenesis, diagnosis, and management. Lancet. 2015;386(10000):1278-1287. doi: 10.1016/S0140-6736(15)00275-5.

11. Schülin S, Schlichting N, Blod C, Opitz S, Suttkus A, Stingu CS, et al. The intra- and extraluminal appendiceal microbiome in pediatric patients: A comparative study. Medicine (Baltimore). 2017;96(52):e9518. doi: 10.1097/MD.0000000000009518.

12. Dethlefsen L, Huse S, Sogin ML, Relman DA. The pervasive effects of an antibiotic on the human gut microbiota, as revealed by deep 16S rRNA sequencing. PLoS Biol. 2008;6(11):e280. doi: 10.1371/journal.pbio.0060280.

13. Stellingwerf ME, Bemelman WA, Löwenberg M, Ponsioen CY, D'Haens GR, van Dieren S, et al. A nationwide database study on colectomy and colorectal cancer in ulcerative colitis: what is the role of appendectomy? Colorectal Dis. 2021;23(1):64-73. doi: 10.1111/codi.15184.

14. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ. 2005;173(5):489-495. doi: 10.1503/cmaj.050051.

15. Sanders NL, Bollinger RR, Lee R, Thomas S, Parker W. Appendectomy and Clostridium difficile colitis: relationships revealed by clinical observations and immunology. World J Gastroenterol. 2013;19(34):5607-5614. doi: 10.3748/wjg.v19.i34.5607.

16. Killinger B, Labrie V. The Appendix in Parkinson's Disease: From Vestigial Remnant to Vital Organ? J Parkinsons Dis. 2019;9(s2):S345-S58. doi: 10.3233/JPD-191703.

17. Swidsinski A, Dörffel Y, Loening-Baucke V, Theissig F, Rückert JC, Ismail M, et al. Acute appendicitis is characterised by local invasion with Fusobacterium nucleatum/necrophorum. Gut. 2011;60(1):34-40. doi: 10.1136/gut.2009.191320.

18. Mandell CH, Garrett WS, Onderdonk AB, Bennett JE, Dolin R, J. BM. Bacteroides, Prevotella, Porphyromonas, and Fusobacterium Species (and other medically important anaerobic Gram-negative bacilli). 8th ed. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. Philadelphia: Elsevier, Saunders; 2015.

19. Peña ME, Sadava EE, Laxague F, Schlottmann F. Usefulness of intraoperative culture swabs in laparoscopic appendectomy for complicated appendicitis. Langenbecks Arch Surg. 2020;405(5):691-695. doi: 10.1007/s00423-020-01913-z.

20. García-Marín A, Pérez-López M, Martínez-Guerrero E, Rodríguez-Cazalla L, Compañ-Rosique A. Microbiologic Analysis of Complicated and Uncomplicated Acute Appendicitis. Surg Infect (Larchmt). 2018;19(1):83-6. doi: 10.1089/sur.2017.210.

21. Reinisch A, Malkomes P, Habbe N, Bechstein WO, Liese J. Bad bacteria in acute appendicitis: rare but relevant. Int J Colorectal Dis. 2017;32(9):1303-1311. doi: 10.1007/s00384-017-2862-0.

22. Schultz J, Freibothe I, Haase M, Glatte P, Barreton G, Ziegler A, et al. Distribution of RET proto-oncogene variants in children with appendicitis. Mol Genet Genomic Med. 2022;10(2):e1864. doi: 10.1002/mgg3.1864.

23. Coldrey E. Treatment of acute appendicitis. British Medical Journal. 1956(2):1458–61.

24. Coldrey E. Five years of conservative treatment of acute appendicitis. J Int Coll Surg. 1959;32:255-61.

25. Bagi P, Dueholm S. Nonoperative management of the ultrasonically evaluated appendiceal mass. Surgery. 1987;101(5):602-605.

26. Crile G. Peritonitis of appendiceal origin treated with massive doses of penicillin; report of 50 cases. Surg Gynecol Obstet. 1946;83:150-162.

27. Salminen P, Paajanen H, Rautio T, Nordström P, Aarnio M, Rantanen T, et al. Antibiotic Therapy vs Appendectomy for Treatment of Uncomplicated Acute Appendicitis: The APPAC Randomized Clinical Trial. JAMA. 2015;313(23):2340-2348. doi: 10.1001/jama.2015.6154.

28. Vons C, Barry C, Maitre S, Pautrat K, Leconte M, Costaglioli B, et al. Amoxicillin plus clavulanic acid versus appendicectomy for treatment of acute uncomplicated appendicitis: an open-label, non-inferiority, randomised controlled trial. Lancet. 2011;377(9777):1573-1579. doi: 10.1016/S0140-6736(11)60410-8.

29. Hansson J, Körner U, Khorram-Manesh A, Solberg A, Lundholm K. Randomized clinical trial of antibiotic therapy versus appendicectomy as primary treatment of acute appendicitis in unselected patients. Br J Surg. 2009;96(5):473-481. doi: 10.1002/bjs.6482.

30. Styrud J, Eriksson S, Nilsson I, Ahlberg G, Haapaniemi S, Neovius G, et al. Appendectomy versus antibiotic treatment in acute appendicitis. a prospective multicenter randomized controlled trial. World J Surg. 2006;30(6):1033-1037. doi: 10.1007/s00268-005-0304-6.

31.DER SPIEGEL (Magazin): Antibiotika machen Blinddarm-OP oft überflüssig. https://www.spiegel.de/gesundheit/diagnose/blinddarmentzuendung-antibiotika-macht-op-oft-ueberfluessig-a-1039024.html (2015). Accessed 6.5.2022.

32. GEO-Magazin: ANTIBIOTIKA ODER OPERATION? Welche Behandlungsmethode bei einer Blinddarmentzündung die richtige ist. https://www.geo.de/wissen/gesundheit/blinddarmentzuendung--ist-immer-eine-op-norwendig--31570748.html (2022). Accessed 2.5.2022.

33. Flum DR, Davidson GH, Monsell SE, Shapiro NI, Odom SR, Sanchez SE, et al. A Randomized Trial Comparing Antibiotics with Appendectomy for Appendicitis. N Engl J Med. 2020;383(20):1907-1919. doi: 10.1056/NEJMoa2014320.

34. Sallinen V, Akl EA, You JJ, Agarwal A, Shoucair S, Vandvik PO, et al. Meta-analysis of antibiotics versus appendicectomy for non-perforated acute appendicitis. Br J Surg. 2016;103(6):656-667. doi: 10.1002/bjs.10147.

35. Davidson GH, Flum DR, Monsell SE, Kao LS, Voldal EC, Heagerty PJ, et al. Antibiotics versus Appendectomy for Acute Appendicitis - Longer-Term Outcomes. N Engl J Med. 2021;385(25):2395-2357. doi: 10.1056/NEJMc2116018.

36. Salminen P, Tuominen R, Paajanen H, Rautio T, Nordström P, Aarnio M, et al. Five-Year Follow-up of Antibiotic Therapy for Uncomplicated Acute Appendicitis in the APPAC Randomized Clinical Trial. JAMA. 2018;320(12):1259-1265. doi: 10.1001/jama.2018.13201.

37. Gorter RR, Eker HH, Gorter-Stam MA, Abis GS, Acharya A, Ankersmit M, et al. Diagnosis and management of acute appendicitis. EAES consensus development conference 2015. Surg Endosc. 2016. doi: 10.1007/s00464-016-5245-7.

38. Di Saverio S, Podda M, De Simone B, Ceresoli M, Augustin G, Gori A, et al. Diagnosis and treatment of acute appendicitis: 2020 update of the WSES Jerusalem guidelines. World J Emerg Surg. 2020;15(1):27. doi: 10.1186/s13017-020-00306-3.

39. Ashley DJ. Observations on the epidemiology of appendicitis. Gut. 1967;8(6):533-538. doi: 10.1136/gut.8.6.533.

40. Kraemer M, Franke C, Ohmann C, Yang Q, Group AAPS. Acute appendicitis in late adulthood: incidence, presentation, and outcome. Results of a prospective multicenter acute abdominal pain study and a review of the literature. Langenbecks Arch Surg. 2000;385(7):470-481. doi: 10.1007/s004230000165.

41. Kotaluoto S, Ukkonen M, Pauniaho SL, Helminen M, Sand J, Rantanen T. Mortality Related to Appendectomy; a Population Based Analysis over Two Decades in Finland. World J Surg. 2017;41(1):64-69. doi: 10.1007/s00268-016-3688-6.

42. Antoniou SA, Mavridis D, Kontouli KM, Drakopoulos V, Gorter-Stam M, Eriksson S, et al. EAES rapid guideline: appendicitis in the elderly. Surg Endosc. 2021;35(7):3233-43. doi: 10.1007/s00464-021-08524-9.

43. Fugazzola P, Ceresoli M, Agnoletti V, Agresta F, Amato B, Carcoforo P, et al. The SIFIPAC/WSES/SICG/SIMEU guidelines for diagnosis and treatment of acute appendicitis in the elderly (2019 edition). World J Emerg Surg. 2020;15(1):19. doi: 10.1186/s13017-020-00298-0.

44. Mende A, Riegel AK, Plümer L, Olotu C, Goetz AE, Kiefmann R. Determinants of Perioperative Outcome in Frail Older Patients. Dtsch Arztebl Int. 2019;116(5):73-82. doi: 10.3238/arztebl.2019.0073.

45. Reinisch A, Heil J, Woeste G, Bechstein W, Liese J. The meteorological influence on seasonal alterations in the course of acute appendicitis. J Surg Res. 2017;217:137-143. doi: 10.1016/j.jss.2017.05.015.

46. Li G, Liu J, Lu H, Hu W, Hu M, He J, et al. Multiple environmental exposures and obesity in eastern China: An individual exposure evaluation model. Chemosphere. 2022;298:134316. doi: 10.1016/j.chemosphere.2022.134316.

47. Münzel T, Gori T, Babisch W, Basner M. Cardiovascular effects of environmental noise exposure. Eur Heart J. 2014;35(13):829-36. doi: 10.1093/eurheartj/ehu030.

48. Zangbar B, Rhee P, Pandit V, Hsu CH, Khalil M, Okeefe T, et al. Seasonal Variation in Emergency General Surgery. Ann Surg. 2016;263(1):76-81. doi: 10.1097/SLA.0000000000001238.

49. Ilves I, Fagerström A, Herzig KH, Juvonen P, Miettinen P, Paajanen H. Seasonal variations of acute appendicitis and nonspecific abdominal pain in Finland. World J Gastroenterol. 2014;20(14):4037-4042. doi: 10.3748/wjg.v20.i14.4037.

50. Deutscher Wetterdienst: Wetterlexikon. https://www.dwd.de/DE/service/lexikon/Functions/glossar.html?lv2=101334&lv3=101452 Accessed 6.5.2022.

51. Durkin MJ, Dicks KV, Baker AW, Lewis SS, Moehring RW, Chen LF, et al. Seasonal Variation of Common Surgical Site Infections: Does Season Matter? Infect Control Hosp Epidemiol. 2015;36(9):1011-1016. doi: 10.1017/ice.2015.121.

52. Bodmann KF, Grabein B. Empfehlungen zur kalkulierten parenteralen Initialtherapie bakterieller Erkrankungen bei Erwachsenen; Update 2010. Chemother J. 2010;19:179–255.

53. Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB, et al. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. Clin Infect Dis. 2009;48(1):1-12. doi: 10.1086/595011.

54. Foo FJ, Beckingham IJ, Ahmed I. Intra-operative culture swabs in acute appendicitis: a waste of resources. Surgeon. 2008;6(5):278-281.

55. Gladman MA, Knowles CH, Gladman LJ, Payne JG. Intra-operative culture in appendicitis: traditional practice challenged. Ann R Coll Surg Engl. 2004;86(3):196-201. doi: 10.1308/003588404323043346.

56. Reinisch A, Schröder SR, Ulrich F, Padberg W, Liese J. Antibiotic-treated acute appendicitis-reception in social media. Langenbecks Arch Surg. 2019;404(3):343-349. doi: 10.1007/s00423-019-01777-y.

57. Bartlett C, Wurtz R. Twitter and public health. J Public Health Manag Pract. 2015;21(4):375-383. doi: 10.1097/PHH.0000000000000041.

58. Wolters Kluwer: Media Kit Annals of Surgery. (2018). Accessed June 6th 2018.

59. Dwan K, Altman DG, Arnaiz JA, Bloom J, Chan AW, Cronin E, et al. Systematic review of the empirical evidence of study publication bias and outcome reporting bias. PLoS One. 2008;3(8):e3081. doi: 10.1371/journal.pone.0003081.

60. Reinisch A, Reichert M, Hecker A, Padberg W, Ulrich F, Liese J. Nonoperative Antibiotic Treatment of Appendicitis in Adults: A Survey among Clinically Active Surgeons. Visc Med. 2020;36(6):494-500. doi: 10.1159/000506058.

61. Yeh DD, Sakran JV, Rattan R, Mehta A, Ruiz G, Lieberman H, et al. A survey of the practice and attitudes of surgeons regarding the treatment of appendicitis. Am J Surg. 2019;218(1):106-12. doi: 10.1016/j.amjsurg.2018.08.019.

62. Reinisch A, Reichert M, Ondo Meva CC, Padberg W, Ulrich F, Liese J. Frailty in elderly patients with acute appendicitis. Eur J Trauma Emerg Surg. 2022;48(4):3033-3042. doi: 10.1007/s00068-022-01878-2.

63. Ältere Menschen - Die Bevölkerungsgruppe der älteren Menschen ab 65 Jahren. https://www.destatis.de/DE/Themen/Querschnitt/Demografischer-Wandel/Aeltere-Menschen/bevoelkerung-ab-65-j.html Accessed 22.5.2022.

64. Statistisches Bundesamt: Eckdaten der Krankenhauspatientinnen und -patienten. https://www.destatis.de/DE/Themen/Gesellschaft-Umwelt/Gesundheit/Krankenhaeuser/Tabellen/entlassene-patienten-eckdaten.html Accessed 12.05.2022.

65. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146-56. doi: 10.1093/gerona/56.3.m146.

66. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet. 2013;381(9868):752-762. doi: 10.1016/S0140-6736(12)62167-9.

67. Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. J Gerontol A Biol Sci Med Sci. 2007;62(7):722-727. doi: 10.1093/gerona/62.7.722.

68. Fransvea P, Fico V, Cozza V, Costa G, Lepre L, Mercantini P, et al. Clinical-pathological features and treatment of acute appendicitis in the very elderly: an interim analysis of the FRAILESEL Italian multicentre prospective study. Eur J Trauma Emerg Surg. 2022;48(2):1177-1188. doi: 10.1007/s00068-021-01645-9.

69. Gilbert T, Neuburger J, Kraindler J, Keeble E, Smith P, Ariti C, et al. Development and validation of a Hospital Frailty Risk Score focusing on older people in acute care settings using electronic hospital records: an observational study. Lancet. 2018;391(10132):1775-1782. doi: 10.1016/S0140-6736(18)30668-8.

70. Velanovich V, Antoine H, Swartz A, Peters D, Rubinfeld I. Accumulating deficits model of frailty and postoperative mortality and morbidity: its application to a national database. J Surg Res. 2013;183(1):104-110. doi: 10.1016/j.jss.2013.01.021.

5. Anhang mit Originalarbeiten

ARTICLE IN PRESS

JOURNAL OF SURGICAL RESEARCH • ■ 2017 (■) 1–7

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.JournalofSurgicalResearch.com

The meteorological influence on seasonal alterations in the course of acute appendicitis

Alexander Reinisch, MD, * *Jan Heil, MD, Guido Woeste, MD, Wolf Bechstein, MD, and Juliane Liese, MD*

Department of General and Visceral Surgery, University Hospital and Clinics, Goethe-University, Frankfurt/Main, Germany

ARTICLE INFO

Article history:
Received 14 January 2017
Received in revised form
16 March 2017
Accepted 2 May 2017
Available online xxx

Keywords:
Appendicitis
Appendectomy
Complications
Seasonal variations
Meteorology

ABSTRACT

Background: Several diseases, including acute appendicitis (AA), have been known to undergo seasonal variations. Changes in the incidence and course of AA are attributed to seasonal weather differences, but this connection remains unproven.

Methods: In this retrospective, single-center analysis, we analyzed daily meteorological data over an 8-year period. A connection of day-by-day meteorological data with 680 consecutive appendectomies was performed. Patients' characteristics, intraoperative findings, and outcome parameters were analyzed. Seasons were classified meteorologically as 3-month periods (winter, spring, summer, and autumn).

Results: Nonambient temperature (unusual warm or cold weather) is correlated with a higher rate of complicated (gangrenous or perforated) AA ($P = 0.018$). In summer and winter, days with nonambient temperatures were more frequent ($P < 0.0001$). A higher rate of complicated AA was seen during summer and winter ($P = 0.009$). In addition, patients operated on in summer and accordingly after warm days suffer more complications ($P < 0.0001$), especially more superficial surgical site infections ($P < 0.048$).

Conclusions: The concordant observation of more complicated AA and complications after AA with meteorological data and calendric seasonal variations makes it most likely that temperature is a cofactor in complicated AA and contributes to the seasonal variations in AA. Although an increase in the microbiome of the skin during warm seasons might explain the increase in surgical site infection, the functional connection between warmer temperatures and AA complications remains unclear.

Introduction

Seasonal variations are known to be associated with several inflammatory and noninflammatory conditions in emergency medicine. These variations were found in stroke and cardiac arrest but also have been described for acute appendicitis (AA) and cholecystitis.[1-3] Seasonal changes apply both to the incidence and the severity of these conditions. Besides seasonal differences in behavior and activity, most authors attribute these effects to meteorological differences. In general emergency surgery, most data on seasonal variations are available for AA.[4-7]

AA is one of the most common inflammatory diseases in acute care units with an incidence of 80-100/100,000.[8] However, despite the fact that surgical research has been focused on AA for over a century, our understanding of the

* *Corresponding author*. Department of General and Visceral Surgery, University Hospital and Clinics, Goethe-University Frankfurt/Main Theodor-Stern-Kai 7 60596 Frankfurt/Main, Tel.: +49 69-6301-6502; fax: +49 69-6301-6211.

E-mail address: alexander.reinisch@kgu.de (A. Reinisch).

0022-4804/$ – see front matter

http://dx.doi.org/10.1016/j.jss.2017.05.015

pathogenesis of the disease remains fragmentary.[9] Still, there is no explanation why the appendix gets inflamed at all and why this inflammation sometimes proceeds to gangrene or perforation of the appendix—the so-called complicated AA. It is known that the outcome after complicated AA is worse than noncomplicated AA.[10]

Little is known about the fundamental connections between monthly, trimestrial, or semi-annual changes in incidence and severity of AA. Although the weather itself has been a suspect in these variations, only a few articles have analyzed meteorological data, and all of these use the monthly averages.[4] Moreover, the results are inconsistent; while some studies see an incidence peak in summer, others see peaks in autumn or winter.[11] Data on the severity and outcome of AA are missing.

The aim of this study was to investigate variations in the clinical course of patients treated for AA. We studied the possible seasonal effects on admission rates, severity, and outcome based on day-by-day meteorological data in ambient meteorological settings.

Methods

All consecutive patients aged 12 years or older and treated for AA between January 1, 2008 and December 31, 2015 were included in this retrospective, single-center study. Exclusion criteria included all intraoperatively diagnosed neoplasms (except neuroendocrine tumors of the appendix below 1 cm [T1]), appendectomies (AEs) performed during operations for another reason and travel through patients (whereabouts of the patients not in Frankfurt/Main, Germany for 24 h prior to admission).

Acquisition of patient's data was approved by the Ethics Committee of the University Hospital of Frankfurt, Germany (Institutional Review Board No 544/15). Meteorological data were received from the German Meteorological Service (Deutscher Wetterdienst, DW, Offenbach).

Calendar data

We analyzed 2922 days. The years and months were defined according to the Gregorian calendar including leap years. The summer half-year was defined as the time span from spring to fall equinox (March 20 to September 22/23), and the winter half-year was from September 23/24 to March 19. Seasons were analyzed by using the meteorological classification: summer meteorological, June 1–August 31; autumn meteorological, September 1–November 30; winter meteorological, December 1–February 28/29; and spring meteorological, March 1–May 31. Daytime was defined as the time span between 6 AM and 6 PM.

Meteorological data

Meteorological data were recorded on a daily, monthly, semi-annual, seasonal, semi-annual (summer half-year and winter half-year), and annual basis by the local survey station within a 5-km radius of the hospital. The data included median/mean, minimal and maximal temperature (°C, ground-level), humidity (relatively), atmospheric pressure (hPa), rainfall (mm/m^2), precipitation (snow, hail), and the duration of sunshine (h) and cloud cover (relatively, 0-8/8). These parameters are defined and described in Table 1.

Warm days (WD) were defined as days with a temperature higher or equal to the mean temperature (MT) plus 1 standard deviation (SD), and hot days (HD) were the mean maximum temperature plus 1 SD. Cold days (CD) and very cold days (VCD) were defined correspondently (CD = MT - 1 SD, VCD = mean minimum temperature - 1 SD). All WD or HD or CD or VCD days were further summarized as nonambient temperature days (NAT). Humid (HUM) and dry (DRY) days were defined as days with a median humidity ± 1 SD. Days were with a high atmospheric pressure (HAP) low (LAP) atmospheric pressure likewise (mean atmospheric pressure ± 1 SD). Cloud cover was classified following aviation meteorology: cloud cover, 0/8–nil significant clouds to 8/8–overcast. A rainy day is defined as a day with ≥0.1 L rain/m^2, a sunny day (SUN) as days with mean sunshine duration + 1 SD. Hail and snow were analyzed on a daily yes/no basis. Meteorological conditions were analyzed solely and in combination (e.g., DRY WD with HAT). If certain conditions (solely or in combination)

Table 1 – Definition of meteorological parameters.

Parameter (abbreviation)	Definition
Semi-annual periods	
Summer half-year	March 20-September 22/23
Winter half-year	September 23/24-March 19
Seasons (meteorological)	
Summer	June 1-August 31
Autumn	September 1-November 30
Winter	December 1-February 28/29
Spring	March 1-May 31
Temperature	
Warm day (WD)	>18.62°C
Hot day (HD)	>24.25°C
Cold day (CD)	<3.78°C
Very cold day (VCD)	<-0.08°C
Nonambient day (NAT)	WD or HD or CD or VCD
Frosty day	<0°C
Humidity	
Dry day (DRY)	60.72%
Humid day (HUM)	86.72%
Atmospheric pressure	
High atmospheric pressure (HAP)	>1011.4 hPa
Low atmospheric pressure (LAP)	<994.73 hPa
Sky	
Sunny day (SUN)	>8.76 h
Cloud cover	0/8-8/8
Precipitation	
Snow	Any
Rainy day	>1 L/m^2 rain
Hail	Frozen precipitation > 5 mm

occurred on < 1% of the study days, then this day was defined as having extraordinary weather conditions (EXT, Table 2). Absolute meteorological conditions were classified according to international meteorological definitions.[12,13]

Patient data

The patient data included demographic, clinical, and pathological features: day and time of presentation in the emergency department, age, gender, body mass index (BMI), comorbidities, previous abdominal surgery, laboratory, radiological results, surgical procedures (laparoscopic *versus* open, extension of operation, special findings, and use of a drainage), intraoperative findings (complicated/perforated appendicitis), peritonitis (classified with Mannheim peritonitis index [MPI]), and complications (surgical site infections [SSIs] according to the Centers for Disease Control and Prevention classification), reintervention, reoperation, readmission, and length of hospital stay.[14,15] The Charlson comorbidity index was used for the general comorbidity assessment of all patients. The follow-up period after the operation was 30 days.[16]

Surgical procedure and histopathology

The standard surgical procedure for suspected AA is laparoscopic AE. A standard three-port laparoscopy with additional trocars as needed was performed. We used a laparoscopic stapling device (Endo-GIA; Covidien or Endopath-ETS; Ethicon) for resection of the appendix and closure of the appendix stump. The use of intraabdominal drainage in patients with peritonitis was left to the surgeon's preference. Perforated and/or gangrenous (necrosis of the appendix) appendix—described by both the pathological results and operative notes—was classified as complicated appendicitis.

All suspected AA cases received a single shot of preoperative antibiotic prophylaxis 30 min prior to skin incision. Cefuroxime 2 g plus metronidazole 500 mg was used in absence of allergies or contraindication.

Statistical analysis

Patient data were merged with meteorological data of the 24 hours prior to presentation. The patient demographics was expressed as the mean ± SD or as the median and range as appropriate. Fisher's exact test respectively. Chi-square test was used to analyze the differences in categorical variables. The Mann-Whitney *U* and Kruskal-Wallis tests were applied for variables that were not normally distributed. To investigate the risk factors for complicated appendicitis, univariate and multivariate log-regression analyses were used. Unless otherwise indicated, all tests were two-tailed, and *P* values < 0.05 were considered to be significant. All data were analyzed with SPSS, version 23 (IBM, Armonk, NY).

Table 2 – Days with extraordinary weather conditions (EXT).

Variables	Days (*n*)
WD + HUM	18
CD + DRY + LAP	7
WD + DRY + HAP	0
WD + DRY + LAP	17
WD + HUM + HAP	3
WD + HUM + LAP	1

Results

During the 2922 days of observation, 688 AEs for AA were analyzed. Eight patients were excluded (one extensive tumor, three missing data, and five patients whose preoperative stay was not in Frankfurt). Demographic and clinical aspects of the cohort are shown in Table 3. Male patients were significantly older (33 *versus* 30 years, *P* < 0.0001), had a higher BMI (24.9 *versus* 23.0 *P* < 0.0001), and less previous abdominal operations in their medical history (16.1% *versus* 10%, *P* = 0.27). Male patients had a more common frequency of localized peritonitis (67.2% *versus* 50.5%, *P* < 0.001), but the MPI as marker of peritonitis severity was lower in males (MPI: 6.7 *versus* 9.3; *P* < 0.001). The rate of generalized peritonitis was equal. There was a slightly higher tendency toward more complicated AA in men (*P* = 0.084). All other intraoperative and outcome parameters were equal. No patients died during hospital stay or during 30-day follow-up.

Comparisons between noncomplicated AA and complicated AA revealed a significantly higher rate of postoperative complications (22.2% *versus* 9.8%, *P* < 0.0001), a higher rate of SSI grade I and II (6% *versus* 3.2%, *P* < 0.0001) and SSI grade III (8.5% *versus* 1.4%, *P* < 0.0001), higher reoperation rate (4.3% *versus* 1.4%, *P* = 0.004), and a longer postoperative stay (5 [0-23] days *versus* 3 [0-17] days, *P* < 0.0001) for complicated AA.

Calendric analysis

There were 347 patients treated during summer half-year *versus* 333 during winter half-year (*P* = 0.896). There were no noticeable differences in patients' characteristics, intraoperative findings, or postoperative course between patients operated in summer half-year and winter half-year.

The seasonal analysis showed more AA during summer (189) *versus* winter (163) and no difference during summer (164) and autumn (164) (*P* = 0.421). The age, gender, BMI, comorbidities, and C-reactive protein (CRP) did not differ significantly. The white blood cell count (WBC) had a strong tendency (*P* = 0.064) toward higher values in summer and winter. There were significantly more complicated AA during summer and winter (21.7% *versus* 13%, *P* = 0.009), and more intraoperative drainages were applied during these seasons. The rate of laparoscopic operations, conversion rate, and peritonitis (rate and severity) did not differ. Postoperatively, patients treated during summer suffered more overall complications (*P* < 0.001) and more SSI grade I and II (9.8% *versus* 5.4%, *P* = 0.048); the rate of SSI grade III and reoperations showed no differences. The mean postoperative stay was longer for patients operated in summer (3.64 ± 2.28 days *versus* 3.14 ± 2.23 days, *P* = 0.004).

Table 3 – Patient characteristics.

Parameter (unit)	Total	Female	Male	P value
n (%)	680/100	299/44	381/56	
Age (range), y	32 (12-77)	30 (15-89)	33 (12-85)	<0.0001
BMI (kg/m^2)	24.3 (10.7-49.8)	23 (10.7-45.1)	24.9 (15-49.8)	<0.0001
CCI	0.15 (0-8)	0.13 (0-4)	0.16 (0-8)	0.322
Previous abdominal OP (*n*/%)	88/13	48/16.2	40/10.5	0.027
WBC (admission) (/nL)	12.6	12.1	13.1	0.099
CRP (admission) (mg/dL)	4.9	4.7	5	0.656
OP technique				
Laparoscopic (*n*/%)	662/97.4	291/97.3	331/97.4	1
Conversion lap to open (*n*/%)	16/2.4	6/2	10/2.6	0.8
Peritonitis				
Local (*n*/%)	401/59	150/50.2	251/67.5	<0.0001
Generalized (*n*/%)	35/5.1	16/5.4	19/5	0.91
MPI	7.73 ± 4.65	9.32 ± 4.72	6.67 ± 4.337	<0.0001
Complicated appendicitis (*n*/%)	117/17.2	43/14.4	74/19.4	0.084
Complications (any) (*n*/%)	81/11.9	41/13.4	40/10.8	0.296
SSI grade I and II (*n*/%)	39/5.7	19/6.4	20/5.2	0.539
SSI grade III (*n*/%)	18/2.6	10/3.3	8/2.1	0.316
Reoperation (*n*/%)	13/1.9	4/1.3	9/2.4	0.406
LOS (mean, postOP/range) (days)	3.26/0-22	3.26/0-22	3.27/0-18	0.878

CCI = Charlson Comorbidity Index; MPI = Mannheim peritonitis index; LOS = length of stay; OP = operation; lap = laparoscopic.

Meteorological analysis

Seasonal analysis revealed more NAT days in summer and winter *versus* spring and autumn ($P < 0.0001$) and more EXT days during summer (26 days) and spring (14 days) *versus* autumn (2 days) and winter (0 day; $P < 0.0001$). Differences in EXT between summer and spring reached significance marginally ($P = 0.051$). Meteorological parameters were tested in single analyses and in all reasonable combinations against recorded patient data.

The patients' characteristics showed significantly higher CRP (2.68 ± 7.87 *versus* 1.51 ± 7.51, $P = 0.034$) and WBC (13.77 ± 4.4 *versus* 12.45 ± 4.72, $P = 0.034$) values in patients presenting after HD and VCD. This effect was even more obvious after CD + HUM (WBC 13.92 ± 5.52 *versus* 12.55 ± 4.68; CRP 4.71 ± 9.94 *versus* 1.6 ± 7.3 $P = 0.031$) and for WBC after NAT days (13.3 ± 4.66 *versus* 12.5 ± 4.67 $P = 0.009$). Interestingly, more patients presented during the night hours after sunny days (70.9% *versus* 61.6%, $P = 0.034$). No further differences in patients' characteristics were noticed.

The intraoperative data showed a significantly higher rate of complicated AA after NAT days (21.07% *versus* 14.17% $P = 0.016$). There were more patients with peritonitis after NAT days; however, the difference was not significant (67% *versus* 64%, $P = 0.38$). Significantly more intraabdominal drainages were placed after NAT days (25% *versus* 18.1% $P = 0.0169$). After HD, more patients had a complicated AA (23.6% *versus* 15.8%, $P = 0.034$) and peritonitis (69.4% *versus* 58.5%, $P = 0.034$). Other meteorological effects on intraoperative findings were not noticeable.

In the postoperative period, we observed more complications after HD, WD, and WD + DRY (HD: 18% *versus* 10.6%, $P = 0.021$; WD: 18.9% *versus* 10.4%, $P = 0.009$; and WD + DRY: 20.3% *versus* 11.1%, $P = 0.037$). While the median postoperative stay was equal in all groups, the mean postoperative stay was longer after HD (3.36 ± 1.96 d *versus* 3.26 ± 2.26 d, $P = 0.091$). Other meteorological parameters had no influence on the postoperative course.

Due to the sample size, a correlation of severity of appendicitis with the extent of deviations from ambient temperature, ambient atmospheric pressure, precipitation, and other meteorological parameters was not possible.

Combined analysis and multivariate analysis

The graphical analysis showed no conspicuous patter of the distribution of AA, the patients' characteristics, laboratory parameters, operative technique, conversion rate, and drainages. Complicated AA showed a two-peaked pattern with one peak from June to August and a second peak from December to January. We found corresponding peaks for NAT days (Fig. 1A) in combined calendric and meteorological analysis. Other meteorological parameters (alone and combined) showed no equivalent pattern; however, the subdivision of NAT in warm and cold days also showed a two-peak pattern (Fig. 1B). Other outcome parameters had no specific graphical pattern. Postoperative complications showed a peak during June and July, which corresponded to a peak for WD/HD in these months and a higher mean temperature (Fig. 1C and D). An analog correlation between SSI I and II and mean temperature respectively WD/HD was observed.

In the multivariate analysis, complicated AA was significantly associated with operation after NAT days (HR: 1.9; 95% CI: 1.22-2.98; $P = 0.007$) and higher age (HR: 1.07; 95%

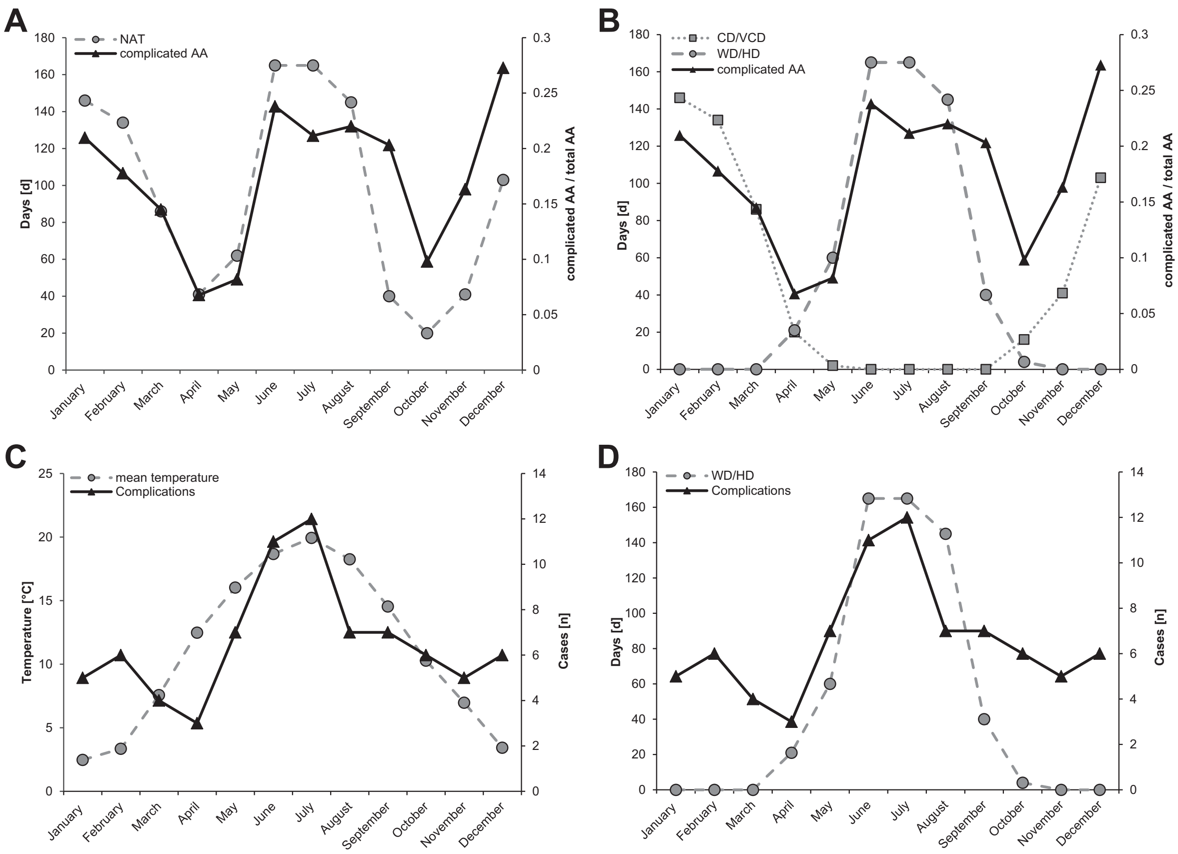

Fig. 1 – Graphical analysis. Complicated AA showed a two-peak pattern during the year and in dependency of NAT days (A) and warm and cold days (B). Postoperative complications were correlated with the mean temperature (C) and showed the highest peak during June and July (D).

CI: 1.05-1.08; $P < 0.0001$), while other factors influencing this parameter could not be identified (Table 4).

Discussion

Seasonal factors can influence both the incidence and course of several acute diseases.[1,3] AA is the most common surgical emergency, and several studies have shown seasonal changes in the incidence of AA. Less data are available on the outcome after AE. Different studies described a maximum incidence during summer months based on large-scale epidemiologic analysis with 60,000 to over 500,000 patients.[3,6,17] A recent study from Sato *et al.* showed a possible correlation between increasing atmospheric pressure and hospital visits for suspected AA but failed to correlate other meteorological factors with AA.[18] This is similar to the findings by Bal *et al.*[11] Our analysis is based on individual patient data and showed a higher rate of AA in summer half-year, but this difference was not significant, most likely to the sample size. There were no differences in incidence between spring and autumn. Our data show significant effects of gender, age, or BMI on the course of the disease, which are in line with actual studies.[19,20] However, these were not of primary interest here.

This article analyses for the first time, the actual meteorological data of the 24 hours prior to admission with the clinical course of the patients. Although we could not show a connection between the incidence of AA and meteorological parameters, our data suggest that seasonal variations in the clinical course of AA might be linked to meteorological variations. The possible link between warmer temperatures and a higher incidence of AA was emphasized by Ilves *et al.* However, study by Ilves *et al.* was limited by the use of pooled average monthly meteorological data; furthermore, the differences in incidence are almost undetectable.[7]

Another study by Wei *et al.* also used the average monthly meteorological numbers, but they also investigated perforation rate of AA. A correlation between temperature and the

Table 4 – Multivariate analysis of perioperative risk factors for complicated appendicitis.

Parameter	Hazard ratio	95% confidence interval	P value
NAT	1.9	1.22-2.98	0.007
Age	1.07	1.05-1.08	<0.0001
Gender	1.29	0.81-2.06	0.276
Body mass index	1.02	0.98-1.02	0.35
CCI	0.925	0.653-0.925	0.653

CCI = Charlson Comorbidity Index; NAT = nonambient temperature.

perforation rate in AA with a maximum during summer was shown.[4] These findings are in contrast to data from other epidemiological studies, in which a maximum of perforated and thereby complicated AA were noticed in winter.[21] Also, in a pediatric study population, Deng *et al*. found higher rates of perforated AA in winter.[22] However, these studies used solely calendric data without attention to the temperature profile or extraordinary weather conditions in this period. Furthermore, none of these studies considered differences of weather conditions within a country or within a larger area. In contrast, we excluded patients who were not present in Frankfurt at least 24 hours prior admission to our university hospital.

We showed a two-peak trend for complicated AA with a maximum in summer and a second peak in winter. Of note, we could show that this pattern is most likely caused by deviations from ambient temperature. The combination of day-by-day meteorological data and calendric data with a concurrent effect on complicated AA may be considered strong evidence that temperature is a cofactor in the pathogenesis of complicated AA. The connection between complicated AA and nonambient temperature is highlighted by adequate observations of other signs of inflammation such as WBC or CRP.

Formerly, the delay between onset of AA and operation was assumed to be a major factor for complicated AA. By now, there is more and more evidence opposing this thesis. Several studies disproved the connection between delayed surgery and perforation.[23] A complicated appendicitis seems to be a distinct subtype of appendicitis, caused by multiple factors. Besides immunologic and genetic factors, the microbiome of the appendicitis might also cause a complicated course.[24] It is unlikely that a delay in treatment caused by special weather is causing an increase in complicated AA as assumed by Wei *et al*.[4] Our data show no connection to frost or precipitation (rain, snow, or hail) or extreme weather conditions and the course of appendicitis. Moreover, a significant delay in presentation for treatment by meteorological conditions can be ruled out by the infrastructural setting of the study hospital (easy accessible via private transport and public transportation, ambulance fully payed by the insurance of all patients in Germany). These are further hints that complicated AA is not just a delayed AA but rather a different disease.

The discrimination between complicated and noncomplicated AA is crucial. Complications including SSIs and the length of stay are worse in patients with complicated AA.[10] This is underlined by our data. Patients with complicated AA suffer more complications—not only relatively benign superficial SSIs but also deep infections. They are more often subjected to repeated operation with longer hospital stays.

Knowledge on seasonal effects of outcome parameters is fragmentary. To the best of our knowledge, our study is the first to show some important connections between seasonal variations and the complications of AE.

Patients treated after warm or hot days suffered more complications especially more SSI grade I and II. The link between SSI and warm temperatures is also described for other operations: Durkin *et al*. conducted two large epidemiologic studies including different surgical procedures (general surgery, gynecological surgery, and spine surgery) in which postoperative SSI showed maximum seasonal variations in summer.[25,26] Our data show for the first time that this observation not only applies to SSI after AE but is also correlated to higher temperatures. One possible explanation is the increase in bacteria population on the skin in warm weather as shown in several studies.[27,28] However, we could not verify this theory due to the retrospective nature of the study and the limited number of patients with SSI. Furthermore, standardized microbiological analysis of all patients was not performed. The examination of microbiological flora in dependency of different weather conditions would be interesting to investigate prospectively.

Limitations of this study include the retrospective character and the limited sample size compared to epidemiological studies. Second, SSI manifests within several days after the operation, and the meteorological data of these days were not included in the analysis. On the other hand, patients remained mainly indoors for the time span of interest and had only limited exposure to environmental effects. Third, there is no valid hypothesis to explain the increase in complicated AA by warm weather. Complicated AA is most likely caused by different factors, and our data suggest that nonambient temperatures contribute to this course of AA. Last, the rate of complicated AA might be influenced by the time lag between onset of symptoms and operation. This period is not analyzed in this study. However, since there is no indication that the presentation of the patients is delayed by the changes in temperature, this bias is not considered significant for the conclusion.

This study correlates high quality, day-by-day meteorological data with detailed patient data. Compared to epidemiological studies, we showed the direct impact of weather factors on this common surgical disease. Besides the unique feature of chronological accuracy, this study also details novel local accuracy *versus* studies using average data for entire regions or countries. We consider our findings to be an important step forward regarding our knowledge of AA as a disease that is far more complex than previously considered.

Conclusions

We observed an association between the course of AA and seasonal variations. A combined analysis of meteorological, calendric, and clinical data shows an increase of complicated AA, most likely caused by nonambient temperatures. This increase contributes to more complications and a longer hospital stay. The present study indicates that meteorological factors affect the course of an important surgical disease.

Acknowledgment

Author's contributions: A.R. contributed in concept, data acquisition, statistics, writing, and final approval. J.H. and G.W. contributed in data acquisition, statistics, critical revision, and final approval. W. B. contributed in writing, critical revision, and final approval. J.L. contributed in concept, data acquisition, writing, critical revision, and final approval.

Disclosure

All the authors declare no conflicts of interest to disclose.

REFERENCES

1. Peckova M, Fahrenbruch CE, Cobb LA, Hallstrom AP. Weekly and seasonal variation in the incidence of cardiac arrests. *Am Heart J*. 1999;137:512–515.
2. Lanska DJ, Hoffmann RG. Seasonal variation in stroke mortality rates. *Neurology*. 1999;52:984–990.
3. Zangbar B, Rhee P, Pandit V, et al. Seasonal variation in emergency general surgery. *Ann Surg*. 2016;263:76–81.
4. Wei PL, Chen CS, Keller JJ, Lin HC. Monthly variation in acute appendicitis incidence: a 10-year nationwide population-based study. *J Surg Res*. 2012;178:670–676.
5. Stein GY, Rath-Wolfson L, Zeidman A, et al. Sex differences in the epidemiology, seasonal variation, and trends in the management of patients with acute appendicitis. *Langenbecks Arch Surg*. 2012;397:1087–1092.
6. Al-Omran M, Mamdani M, McLeod RS. Epidemiologic features of acute appendicitis in Ontario, Canada. *Can J Surg*. 2003;46:263–268.
7. Ilves I, Fagerström A, Herzig KH, Juvonen P, Miettinen P, Paajanen H. Seasonal variations of acute appendicitis and nonspecific abdominal pain in Finland. *World J Gastroenterol*. 2014;20:4037–4042.
8. Coward S, Kareemi H, Clement F, et al. Incidence of appendicitis over time: a Comparative analysis of an Administrative Healthcare Database and a Pathology-Proven appendicitis registry. *PLoS One*. 2016;11:e0165161.
9. Pilcher LS. The treatment of appendicitis by Early laparotomy. *Ann Surg*. 1889;10:434–437.
10. Feng C, Anandalwar S, Sidhwa F, et al. Beyond perforation: influence of peritoneal contamination on clinical severity and resource utilization in children with perforated appendicitis. *J Pediatr Surg*. 2016;51:1896–1899.
11. Bal A, Ozkececi ZT, Turkoglu O, et al. Demographic characteristics and seasonal variations of acute appendicitis. *Ann Ital Chir*. 2015;86:539–544.
12. Deutscher Wetterdienst *Wetterlexikon*. Germany: DWD Offenbach; 2017. http://www.dwd.de/lexikon. Accessed February 8, 2017.
13. Henson R, Ahrens CD. *Meteorology Today*. 11 ed. Boston, MA: Brooks/Cole Publishing; 2015.
14. Linder MM, Wacha H, Feldmann U, Wesch G, Streifensand RA, Gundlach E. [The Mannheim peritonitis index. An instrument for the intraoperative prognosis of peritonitis]. *Chirurg*. 1987;58:84–92.
15. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. *Am J Infect Control*. 1988;16:128–140.
16. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373–383.
17. Addiss DG, Shaffer N, Fowler BS, Tauxe RV. The epidemiology of appendicitis and appendectomy in the United States. *Am J Epidemiol*. 1990;132:910–925.
18. Sato Y, Kojimahara N, Kiyohara K, Endo M, Yamaguchi N. Association between climatic elements and acute appendicitis in Japan. *J Surg Res*. 2016;211:64–69.
19. Bliss LA, Yang CJ, Kent TS, Ng SC, Critchlow JF, Tseng JF. Appendicitis in the modern era: universal problem and variable treatment. *Surg Endosc*. 2015;29:1897–1902.
20. Horvath P, Lange J, Bachmann R, Struller F, Königsrainer A, Zdichavsky M. Comparison of clinical outcome of laparoscopic versus open appendectomy for complicated appendicitis. *Surg Endosc*. 2017;31:199–205.
21. Lee JH, Park YS, Choi JS. The epidemiology of appendicitis and appendectomy in South Korea: national registry data. *J Epidemiol*. 2010;20:97–105.
22. Deng Y, Chang DC, Zhang Y, Webb J, Gabre-Kidan A, Abdullah F. Seasonal and day of the week variations of perforated appendicitis in US children. *Pediatr Surg Int*. 2010;26:691–696.
23. Almström M, Svensson JF, Patkova B, Svenningsson A, Wester T. In-hospital surgical delay does not increase the risk for perforated appendicitis in children: a single-center retrospective cohort study. *Ann Surg*. 2017;265:616–621.
24. Livingston EH, Woodward WA, Sarosi GA, Haley RW. Disconnect between incidence of nonperforated and perforated appendicitis: implications for pathophysiology and management. *Ann Surg*. 2007;245:886–892.
25. Durkin MJ, Dicks KV, Baker AW, et al. Postoperative infection in spine surgery: does the month matter? *J Neurosurg Spine*. 2015;23:128–134.
26. Durkin MJ, Dicks KV, Baker AW, et al. Seasonal variation of common surgical site infections: does season matter? *Infect Control Hosp Epidemiol*. 2015;36:1011–1016.
27. Wang X, Towers S, Panchanathan S, Chowell G. A population based study of seasonality of skin and soft tissue infections: implications for the spread of CA-MRSA. *PLoS One*. 2013;8:e60872.
28. McBride ME, Duncan WC, Knox JM. The environment and the microbial ecology of human skin. *Appl Environ Microbiol*. 1977;33:603–608.

Int J Colorectal Dis
DOI 10.1007/s00384-017-2862-0

ORIGINAL ARTICLE

Bad bacteria in acute appendicitis: rare but relevant

Alexander Reinisch [1] · **Patrizia Malkomes** [1] · **Nils Habbe** [1,2] · **Wolf Otto Bechstein** [1] · **Juliane Liese** [1]

Accepted: 7 July 2017

Abstract
Purpose Bacterial infections are a factor for morbidity in patients with acute appendicitis (AA). The spreading of multidrug-resistant (MDR) bacteria is a significant problem in surgery, and the most relevant MDR pathogens are summarized as *Enterobacteriaceae*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterococci* (ESKAPE) bacteria. Data regarding the species and distribution of bacteria in AA are available, but information about the resistances and their relevance is deficient.
Methods In this retrospective study, we analyzed microbiological swabs of patients with AA. The outcome parameters of patients after laparoscopic appendectomy were analyzed against microbiological results, including antibiotic resistance testing. Positive swabs were compared with bacteria cultivated after alternative abdominal emergency surgery (AES).
Results In total, 584 patients with AA were included and had a mean age of 35.5 years. In 216 patients (36.9%), a swab was taken, and in 128 (59.3%) swabs, bacteria could be cultivated. The most frequent organisms were *Escherichia coli*, *Bacteroides* species, and *Pseudomonas*. In 9.4% of the positive AA swabs, MDR germs were cultivated, and all of them were ESKAPE pathogens. Patients with MDR bacteria in AA suffered more infectious complications ($p = 0.006$) and needed longer hospitalizations ($p < 0.009$). In AES, aside from appendicitis, a different spectrum containing more MDR bacteria was cultivated (5.9 vs. 20.9%; $p < 0.0001$).
Conclusions Although they occur less frequently in appendectomy compared to emergency surgeries for other abdominal diseases, MDR bacteria are traceable in this common disease and contribute to additional morbidity.

Keywords Appendicitis · Multidrug-resistance · ESKAPE · Bacterial infection

Introduction

Although the pathogenesis of acute appendicitis (AA) is not completely understood, it can be assumed that bacterial infections are a significant factor for morbidity in patients with AA [1]. Antibiotic treatment for uncomplicated appendicitis is just emerging, but appendectomy (AE) is still the first-choice treatment for AA, particularly for complicated AA [2]. AE can be performed laparoscopically, and laparoscopic appendectomy (LA) provides advantages over conventional AE, especially in regard to surgical site infections (SSIs) [3]. Complicated AA is not a criterion for exclusion on behalf of LA, but it may be associated with an increasing number of postoperative intra-abdominal infectious complications [4]. Bacterial intra-abdominal infections contribute to the postoperative morbidity in AE, namely infectious complications. Antibiotics play a distinct role in the prevention and therapy of those complications.

The peri- and postoperative use of antibiotics during surgery for AA is mainly empirical. Although several guidelines recommend a selection of antibiotics, they remain vague regarding the choice, duration, and indication for antibiotic

Electronic supplementary material The online version of this article (doi:10.1007/s00384-017-2862-0) contains supplementary material, which is available to authorized users.

✉ Alexander Reinisch
alexander.reinisch@kgu.de

1 Department of General and Visceral Surgery, University Hospital Frankfurt, Goethe University, Theodor-Stern-Kai 7, 60590 Frankfurt, Germany

2 General Surgery and Coloproctology, DKD HELIOS Klinik Wiesbaden, Aukammallee 33, 65191 Wiesbaden, Germany

Published online: 15 July 2017

therapy, and multidrug-resistant (MDR) bacteria are not a frequent focus [5–7]. Despite the effectiveness of the empirical approach, a significant proportion of surgeons collect microbiological swabs during AE to gather information on the bacterial spectrum and resistances, but the consequences of these microbiological examinations remain unclear [8]. There are data regarding bacteria that are commonly found in AA. However, the observational studies on this topic have multiple restrictions; moreover, only isolated studies have analyzed the MDR bacteria associated with AA [9].

The most relevant MDR bacteria, namely *Enterobacteriaceae*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterococci*, with distinct drug resistances have been summarized under the keyword ESKAPE [10]. The importance and increasing incidence of these pathogens has been shown, and according to some authors, the empirical use of antibiotic drugs contributes to this problem [11–13]. Consequently, in AA, we are confronted with a lack of knowledge regarding important aspects of the microbiome's influence on the disease. Furthermore, the information about MDR bacteria in AA is fragmentary. Against this background, it is inapprehensible that microbiological testing during AE is questioned. Arguments against taking swabs during AE are that the microbiological spectrum is widely known, that the results of the microbiological cultures do not influence the patient's treatment, and that the outcomes and processing of the swabs take too long [14–17].

The aim of this retrospective study was to analyze the microbiological spectrum in AA, with a special focus on MDR pathogens. In this study, AE was performed in a highly standardized perioperative setting with clear conditions for collecting microbiological swabs and in accordance with the national guidelines regarding perioperative antibiotic treatment. The unselected AE cohort was compared with randomly selected microbiological cultures from patients after emergency surgery for alternative reasons in the same period.

Patients and methods

This retrospective analysis was approved by the local Ethics Committee of the University Hospital of Frankfurt, Germany (Institutional Review Board No. 544/15). This single-center study included all consecutive patients who were operated on for appendicitis between 2008 and 2014. Data collected included demographic and clinical-pathological features, specifically age, gender, body mass index (BMI), comorbidities, previous abdominal surgery, laboratory results, surgical procedures, complication rates (especially SSIs according to the CDC classification and additional infectious complications), length of hospital stay (LOS), readmission, re-intervention, reoperation, and pathological and microbiological findings [18]. The Charlson Comorbidity Index (CCI) was used for the general risk assessment of all patients [19]. AEs that were performed during operations for another reason and cases in which a neoplasm other than a neuroendocrine tumor of the appendix below 1 cm (T1) was detected during the operation were excluded.

For microbiological comparison, swabs from patients undergoing alternative abdominal emergency surgery (AES) for alternative reasons were analyzed. These patients were subgrouped with those operated on for a community-acquired pathology (COM; except AA; e.g., cholecystitis, diverticulitis of the colon, perforations, abdominal trauma) and those operated on for hospital-acquired peritonitis (HOS; hospitalization >24 h prior to operation, e.g., anastomotic leakage, burst abdomen, bleeding with peritonitis).

The follow-up period after the operation was at least 30 days.

Surgical procedure and histopathology

All patients with suspected appendicitis were scheduled for laparoscopic appendectomy, if possible. A standard three-port laparoscopy was performed; closure of the appendix stump was executed using a laparoscopic stapling device [Endo GIA™ (Covidien, Dublin, Ireland) or Endopath ETS® (Ethicon, Somerville, NJ, USA)].

Signs of peritoneal inflammation and peritoneal cavity fluid in the lower right quadrant and/or the recto-vesical or recto-uterine pouch were classified as local peritonitis, whereas inflammation or peritoneal cavity fluid in the lower left or the upper quadrants was classified as generalized peritonitis. The absence of abdominal fluid and the restriction of inflammation to the mesoappendix or the periappendicular tissue were classified as the absence of peritonitis. In patients with local and generalized peritonitis, the Mannheim Peritonitis Index (MPI) was recorded [20].

All patients with peritonitis received peritoneal lavage and suction of as much peritoneal cavity fluid as possible. The use of intra-abdominal drainage in patients with peritonitis was left to the surgeon's preference.

A perforated and/or gangrenous (necrosis of the appendix) appendix, described both by pathological results and operative notes, was classified as complicated appendicitis [21]. Perforation that was described in the operative notes and the pathological results was classified as macroperforation, whereas perforation that was only visible during the pathological workup was considered microperforation.

Microbiological analysis and antibiotic therapy

In patients with cloudy abdominal fluid or perforation, a microbiological swab was obtained either by laparoscopic direct swab or by sampling from the laparoscopic suction via a sterile "fluid trap." In open surgery or after conversion and AES, direct swabs were taken. Until cultivation, the swabs were stored in a Transystem® AMIES agar gel (COPAN, Brescia, Italy). All swabs were cultivated by the Institute for Medical Microbiology and Infection Control (Prof. V. Kempf) using routine methods. Cultivated bacteria and fungi were recorded and tested against antibiotics and antifungal drugs commonly used in our department. All microbiological results were received electronically, and if MDR pathogens were detected, an additional notice was received by telephone as soon as the data were available.

According to the Infectious Diseases Society of America, all *Enterobacteriaceae*, *S. aureus*, *K. pneumoniae*, *Acinetobacter baumannii*, *P. aeruginosa*, and *Enterococci* with distinct drug resistances were classified as ESKAPE bacteria [10].

As a standard practice in our department, all patients who receive operations for suspected or confirmed intra-abdominal infections receive a single shot of preoperative antibiotic prophylaxis (PAP) 30 min prior to skin incision.

The indications for postoperative antibiotic therapy were large amounts of cloudy abdominal fluid, pus, or stool; severe peritoneal inflammation, either locally or generalized; persistent postoperative fever; significantly elevated white blood cell counts or C-reactive protein (CRP) levels; and an elevated white blood cell (WBC) count at admission.

For each positive swab in AA patients, a swab from patients with alternative AES was selected, with alternating swabs from COM and HOS peritonitis. The selection was performed electronically using a random generator algorithm.

Statistical analysis

The patient demographics were expressed as the mean ± standard deviation or as the median and range, as appropriate. Fisher's exact test was used to analyze the differences in categorical variables for predicted values <5; otherwise, the two-sided chi-square test was used. For variables that were not normally distributed, the Mann-Whitney *U* and Kruskal-Wallis tests were applied. A multivariate analysis of variance resp. multivariate regression analysis was conducted, as appropriate.

Unless indicated, all tests were two-tailed, and p values <0.05 were considered significant.

All data analyses and random data selections were performed using SPSS, version 23 (IBM, Armonk, NY, USA).

Results

Patient characteristics and surgical procedure

Between January 2008 and December 2014, 590 patients were operated on for suspected or confirmed acute appendicitis and were retrospectively assessed for eligibility. Six patients were excluded (three with an intraoperative diagnosis of extensive malignancy and three because of missing data). Seven more patients were lost to follow-up.

In total, 584 patients (255 women and 329 men) were included. The patient demographics are shown in Table 1. The mean age was 35.5 years (12–89 years), and the mean BMI was 24.9 kg/m^2. Overall, 92% of the patients had no comorbidities, and 67% had no previous abdominal operations.

An ambiguous clinical presentation necessitated a preoperative CT scan in 169 (28.9%) patients. A single shot of PAP 30 min prior to incision was administered in 576 (98.6%) patients. According to the recommendations of the Paul-Ehrlich-Society, cefuroxime in combination with metronidazole was used in 531 (90.9%) patients [5]. Because of intolerance and allergies, 39 (6.7%) patients received alternative antibiotics of comparable potency (combinations of ciprofloxacin, cefazolin, amoxicillin + clavulanic acid, and clindamycin). Four patients received carbapenems, and two

Table 1 Characteristics of the study cohort

	Total group, *n* = 584
Age, years (range)	35.5 (12–89)
Gender, *n* (%)	
Male	255 (43.7)
Female	329 (56.3)
Body mass index, kg/m^2	24.93 (13.6–49.8)
Laboratory results	
C-reactive protein <0.5 mg/dl (±SD)	4.99 (7.84)
White cell count 4.2–10/nl (±SD)	12.73 (4.47)
Previous abdominal surgery, *n* (%)	
Yes	80 (13.5)
No	392 (67.1)
Unknown	112 (19.3)
Charlson Comorbidity Index (CCI), *n* (%)	
0	540 (92.5)
1	30 (5.1)
2	6 (1.0)
3	4 (0.7)
>4	4 (0.7)
Pre-existing diseases, *n* (%)	
Hemostatic disorders	6 (1.0)
Crohn's disease	5 (0.9)
Ulcerative colitis	1 (0.2)
HIV	3 (0.5)
Single-shot preoperative antibiotic prophylaxis, *n* (%)	576 (98.6)
Surgical procedure, *n* (%)	
Laparoscopic	567 (97.1)
Open	17 (2.9)
Conversion laparoscopic to open	12 (2.1)
Length of hospital stay, days	3.7 (1–34)

patients received piperacillin + tazobactam prior to the operation, administered by the referring department.

A laparoscopic approach was performed in 567 (97.1%) of the patients. In six patients (1.0%), we performed an emergency laparotomy because abdominal sepsis and intraoperative appendicitis were detected. In six more patients (1.0%), the surgeon chose a primary open approach because of extensive previous abdominal operations, and in five (0.9%) cases, because of the patient's preferences. Conversion from laparoscopic to open appendectomy was necessary in 12 (2.1%) patients.

The responsible surgeon prescribed postoperative antibiotic therapy after the evaluation of systemic inflammation, intraoperative findings, and comorbidity of the patients.

Postoperative antibiotic therapy was administered in 224 (38.4%) of the patients. Of these, 202 (90.18%) received cefuroxime and metronidazole, with additional doxycycline in 18 women with co-existing adnexitis. Four patients received postoperative carbapenems; all of them had previously received this type of antibiotic preoperatively. Antifungal drugs were not administered.

Histopathology and clinical course

Appendicitis was confirmed in 522 (89.4%) patients in the histopathological examination; thus, the negative appendectomy rate was 10.6%. In five (8.7%) of the 57 appendices without signs of inflammation, the pathologic findings revealed *neurogenic appendicitis*, which reduced the negative appendectomy rate to 9.8%.

The criteria for complicated appendicitis were fulfilled in 99 (17%) of the patients (perforated or gangrenous). Peritonitis was found in 391 (66.9%) of the patients by the time of surgery. In most cases (n = 355, 90.8%), the peritonitis was local; generalized peritonitis was found in 9.2% (n = 36) of the patients. Patients with complicated appendicitis had a significantly higher MPI compared to the uncomplicated group (9 vs. 7; p = 0.003).

The patient characteristics and clinical outcomes among patients with uncomplicated and complicated appendicitis are listed in Table 2. Interestingly, patients with complicated appendicitis were significantly older and had a significantly higher BMI. Although the rate of surgical site infections and of re-operations did not differ, the overall complication rate was significantly higher in patients with complicated appendicitis (p = 0.038). These findings correlated with a significantly longer LOS of 5.2 (±3.4) days in patients with complicated appendicitis compared with 3.4 (±2.4) days in uncomplicated patients (p < 0.0001).

Six (1%) patients were readmitted during the 30-day follow-up period, four of them because of infectious complications (two patients with an intra-abdominal abscess and two patients with grade II SSI). In both patients with an intra-abdominal abscess, interventional abscess drainage was applied. In patients with grade II SSI, wound revision under local anesthesia was performed. All patients were discharged after an uneventful course within 2 to 6 days.

Table 2 Clinical outcome of patients with uncomplicated and complicated appendicitis

	Uncomplicated appendicitis, n = 485	Complicated appendicitis, n = 99	p
Female/male, n	218:267	37:62	n.s.
Age, years	33.2	46.4	<0.0001
Body mass index, kg/m^2	24.7	26.3	0.001
Overall complications, n (%)	50 (10.3)	18 (18.2)	0.038
Surgical site infections, n (%)			n.s.
I	7 (1.4)	1 (1)	
II	11 (2.2)	5 (5)	
III (intra-abdominal abscess)	7 (1.4)	3 (3)	
Re-operation, n (%)	9 (1.9)	2 (2)	n.s.
Mannheim Peritonitis Index (MPI)	7.21	8.99	0.003
Swabs taken, n (%)			
Positive swabs	146 (30.1)	70 (70.7)	
Number of organisms	71 (48.6)	57 (81.4)	
1 organism	45 (63.3)	23 (40.4)	<0.0001
2 organisms	16 (22.5)	26 (45.6)	<0.0001
3 organisms	10 (14.1)	8 (14.0)	<0.0001
Postoperative length of hospital stay (days)	2	4	<0.0001

n.s. no significance

Microbiological analysis

In 216 (36.9%) patients with cloudy abdominal fluid, abscesses, or macroperforation, a microbiological swab was taken; 41% (n = 88) of the swabs were sterile. Significantly more swabs were taken in patients with complicated AA compared with non-complicated AA (70.7 vs. 30.1%; $p < 0.001$) and swabs were more often positive in complicated AA (81.4 vs. 48.6; $p < 0.001$; Table 2).

In total, 205 bacteria were isolated and cultivated in 128 swabs in AA and compared with 203 bacteria from 128 swabs in AES. Antibiotic susceptibility testing (AST) was performed on all cultivated organisms. A maximum of three different genera of bacteria were found per patient in AA, four in smears from AES. Supplementary Table 1 shows the different isolated bacteria of the abdominal fluid in AA. The most frequently cultured organisms in AA were *Escherichia coli*, *Bacteroides* species, and *P. aeruginosa*. Fungi were isolated from the swabs of six patients (1.2%; five *Candida albicans*, one Geotridium species). Only in one patient was the fungus the only isolated organism.

The comparison of the microbiome in AA and AES surgery revealed noticeable differences (Table 3). Although the number of swabs with more than two germs was comparable (AA: n = 13, AES: n = 16), more fungi were cultivated in COM or HOS peritonitis (AA: n = 6 vs. COM: n = 11 and HOS: n = 27; p = 0.009 and $p < 0.0001$).

In AA and COM, the most frequently cultivated germ was *E. coli* (AA 44.9%; COM 26.7%) followed by *Enterococcus faecalis* (15.2%); in HOS, *Enterococcus* (30.6%) was more frequent than *E. coli* (20.4%). All differences were significant ($p < 0.009$). The distributions of *K. pneumoniae* and *P. aeruginosa* were similar. There were significantly fewer *Bacteroides* spp. in AES peritonitis compared with AA (5.9 vs. 19.4%; $p < 0.0001$).

All the MDR bacteria cultivated from swabs after AA and AES (COM and HOS) peritonitis were ESKAPE bacteria.

After AES, significantly more ESKAPE pathogens were cultivated compared with AA (AES 20.9 vs. AA 5.9% of isolated germs; $p < 0.0001$). ESKAPE bacteria were found in significantly more smears after HOS or COM compared with AA, but the difference between HOS and COM was not statistically significant (HOS 26 MDRs in 64 smears; COM 16 MDRs in 64 smears; AA 1 MDR in 128 smears, $p = 0.0075/p < 0.0001$). *Acinetobacter baumannii* was cultivated only after COM and HOS (one each), and only after HOS was this bacterium MDR classified as an ESKAPE pathogen. The second remarkable pathogen found only after AES was *Clostridium perfringens* in one smear but without clostridial myonecrosis.

Comparing AA patients with sterile swabs to those with positive swabs, we observed marginal significance (p = 0.051) toward more infectious complications and a significantly prolonged stay (median LOS sterile 3.4 days vs. positive 4.68 days, p = 0.027) in patients with positive swabs (Table 4). However, in the multivariate analysis, positive swabs could not be identified as an independent risk factor for postoperative complications and LOS (p = 0.061).

In AA patients with cultivated MDR bacterial infectious complications (p = 0.009), grade I and II SSI (p = 0.005) as

Table 3 Comparison of the microbiome in smears after acute appendicitis (AA) and surgery for alternative abdominal emergency surgeries (AESs)

	AA	AES		*p*
		COM	HOM	AA vs. AES
Bacteria, *n*	205	204		
		105	99	
ESKAPE, *n* (%)	12 (5.8)	44 (21.6)		<0.0001
		16	28	
E. coli, *n* (%)	92 (44.9)	48 (23.5)		<0.0001
		28	20	
Enterococcus faecalis, *n* (%)	3 (1.5)	36 (17.6)		<0.0001
		16	30	
Pseudomonas aeruginosa, *n* (%)	14 (6.8)	11 (5.4)		0.52
		6	5	
Klebsiella pneumoniae, *n* (%)	6 (2.9)	13 (6.4)		0.09
		9	4	
Bacteroides spp., *n* (%)	42 (20.5)	11 (5.4)		<0.0001
		8	3	
Fungi, *n* (%)	6 (2.9)	38 (18.6)		<0.0001
		11	27	

COM community-acquired peritonitis, *HOS* hospital-acquired peritonitis, *ESKAPE* multidrug-resistant *Enterobacteriaceae*, *Staphylococcus aureus*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterococci*

Table 4 Clinical outcome in relation to the detection of multidrug-resistant (MDR) pathogens

	Total	Infectious complication (any) [*n*/%]		Grade I or II SSI [*n*/%]		Grade III SSI [*n*/%]		LOS [median]
	n	*n*	%	*n*	%	*n*	%	*n*
Smears with ESKAPE bacteria	12	4	33	3	25	1	8.3	7
Smears without ESKAPE bacteria	116	9	7.8	4	3.5	4	3.5	4.7
Sterile smears	88	3	3.4	3	3.4	0	0	3.4
No smear	368	24	6.5	13	3.5	4	1.1	2
p (ESKAPE vs. sterile)		0.009		0.005		0.005		0.009
p (ESKAPE vs. no ESKAPE)		0.006		0.0018		0.39[a]		0.129
p (no ESKPAE vs. sterile)		0.157		0.22		0.12		0.029
p (positive smear vs. sterile)		0.051		0.105		0.12[a]		0.027
p (ESKAPE vs. no smear)		0.0005		0.0036		0.03		<0.0001
p (no ESKAPE vs. no smear)		0.64		0.96		0.08		<0.0001
p (sterile vs. no smear)		0.26		0.96		1[a]		0.014

SSI surgical site infection, *LOS* length of hospital stay, *ESKAPE Enterobacteriaceae*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterococci* with multidrug resistance

[a] Fisher's exact test

well as intra-abdominal abscesses (grade III SSI, $p = 0.005$) were observed significantly more frequently than in those with sterile swabs (Table 4). The postoperative stay in AA patients with MDR bacteria was prolonged (sterile 3.4 days vs. MDR 7 days, $p = 0.009$). In the multivariate analysis, the significant difference in intra-abdominal abscesses between the sterile and MDR AA groups diminished ($p = 0.078$), whereas the other differences remained significant (infectious complications, $p = 0.014$; grade I and II SSI, $p = 0.025$; LOS, $p = 0.004$). Between patients with and without MDR in their positive swabs, we observed more infectious complications ($p = 0.006$) and more grade I and II SSI ($p = 0.0018$), but the differences in grade III SSI and LOS did not reach significance.

The comparison of patients with and without smears shows a prolonged stay in patients with smears, regardless of whether they were sterile or included germs ($p < 0.014$). The LOS was prolonged even more if germs were detected, and was longest in patients with ESKAPE germs.

In 36 of the patients with AA germs resistant to the PAP and the first-line postoperative antibiotic therapy (cephalosporin and/or penicillin ± β-lactamase inhibitor and/or quinolone) were found, and 14 of them had limited resistance patterns (no MDR). Postoperative complications of the latter 14 patients did not differ from those with sterile smears or smears with germs not resistant to the PAP.

Of the 12 patients with MDR bacteria, ten received postoperative antibiotic therapy. Whereas one already had received a suitable carbapenem, three more needed a change in antibiotic regime after the AST results were received.

The processing of bacteria, cultivation, and AST after AE required a mean of 3.2 days (range 2–19), and 94% of all swabs were processed in less than 6 days. The time necessary to process the swabs did not differ significantly between samples in which one, two, three, or no bacteria were detected. Sterile findings were released slightly earlier than those of non-sterile swabs (median 2.48 vs. 2.97 days, $p = 0.221$). The overall mean LOS after AE was 3.4 days. Comparing the LOS with the time of release of the microbiological results showed that 46.7% of the patients had already been discharged when the microbiological results were analyzed, and in another 27.1%, the microbiological results were available on the date of discharge.

Discussion

The routine collection of peritoneal swabs for microbiological cultivation from patients with AA is controversial, although it has been performed for decades and still is standard in many hospitals [14–17, 22]. The spectrum of organisms is supposedly well known, consisting of *E. coli*, *Bacteroides*, and a mixture of other representatives of gut flora as well as pathogens such as *Pseudomonas* or *Klebsiella* species on occasion [8]. Further, data on antibiotic resistance and influences of the microbiome on the clinical course in AA is fragmentary to non-existent. The knowledge of infectious pathogens in AA derives from observational studies, most of which were restricted to subtypes of AA such as pediatric patients, perforated AA, or patients with severe intra-abdominal inflammation [9]. Nevertheless, the use of microbiological cultures in AE is questioned or even considered a waste of resources by some researchers [15, 22].

Today, surgeons are increasingly challenged by infections with MDR pathogens [23]. The focus of this retrospective study was to gain information about the frequency and relevance of MDR bacteria in patients who were operated on for AA. In a three-step approach, we first described the microbiome in AA with special attention to MDR germs. Second, we compared our findings to the microbiome found in emergency operations for alternative abdominal pathologies. In the last and third step, we examined the influence of MDR bacteria in AA on outcome parameters.

Our study describes for the first time the microbiome in a cohort of non-selected patients who were treated by laparoscopic AE in a standardized setting of PAP, retrieving and processing of swabs, and postoperative antibiotic therapy, if deemed necessary.

The overall rate of positive swabs in our cohort was high, at 59.3%, compared with other studies of comparable design [15, 22]. Not surprisingly, we found that *E. coli* and *Bacteroides* species were the most common organisms. More interestingly, the spectrum of other bacteria was rather broad compared with that of other studies [24, 25]. Also, we cultivated some rarely found organisms, e.g., *Comamonas testosteroni* and *Micrococcus luteus*.

In addition to naming and classifying the germs isolated in AA, the antibiotic resistance of these pathogens is of the greatest interest. The actual, large-scale study by Coccolini et al. [9] on resistant bacteria in AA provides information on factors associated with MDR. However, this study gives no information on the clinical course of patients with or without MDR after AE and is restricted to severe intra-abdominal inflammation. Other studies are limited to gram-negative bacteria expressing extended spectrum beta-lactamase (ESBL) [17, 26]. In this study, we chose a broader spectrum of germs as potential problematic MDR bacteria: the ESKAPE group of pathogens. Similar to other researchers, we consider these bacteria to be a significant burden [10, 13]. In our study, in 5.8% of the bacteria resp. in 9.4% of the positive swabs, we isolated ESKAPE germs. This is well within the rates published for MDR bacteria in Europe [17]. By examining germs other than ESBL, we could show important associations between MDR germs and the clinical course of the patients: First, the presence of ESKAPE bacteria in swabs doubles the LOS of patients compared to those with sterile swabs. Possibly due to the limited number of patients, the difference in LOS between patients with ESKAPE germs and positive smears without MDR bacteria did not reach significance. Second, patients with MDR bacteria in their smears suffer from infectious complications more frequently. In particular, the rate of infectious complications, primarily grade I and II SSI, was significantly increased by ESKAPE bacteria compared with patients who did not have ESKAPE germs and sterile swabs. The multivariate analysis indicated that infection with ESKAPE germs is an independent risk factor for postoperative infectious complications in our cohort ($p = 0.013$). To our knowledge, our study is the first to show this relevant impact of the microbiome and its resistance pattern on the clinical outcome. The stability of the observations in the multivariate analysis suggests that the MDR status of isolated germs is an additional factor in the course of AA.

One must discuss infectious complications in AE against the background of PAP and postoperative antibiotic therapy. PAP significantly reduces the postoperative infections compared with placebo in patients with AA [1]. In this study, a single shot of preoperative antibiotic prophylaxis was administered in nearly 99% of the patients. The overall rate of infectious complications was low (6.8%). We cultivated bacteria that were resistant to the PAP in 36 of the patients, including 12 with ESCAPE germs. In the latter group, PAP and postoperative antibiotic therapy were ineffective, and infectious complications were found significantly more frequently.

Although this procedure is questioned in AA, in emergency surgery for alternative abdominal pathologies, retrieving peritoneal cultures is an established maneuver, and retrieving cultures under certain conditions is recommended in the relevant guidelines [6]. We compared the microbiome of patients with AA to smears from AES. Interestingly, there were noticeable differences between AA and AES. Other than residencies, the distribution of germs in intra-abdominal infections differs; in our study, we observed a higher rate of *Enterococci* and a lower rate of *Bacteroides* spp. in AES. Whereas *Bacteroides* spp. are considered a less virulent pathogen, *E. faecalis* surely are not. *Enterococcus* is a typical organism in intra-abdominal infections and has an increasing incidence of postoperative and nosocomial acquired infections [27]. *Enterococci* are responsible for up to 12% of SSIs after abdominal operations [28, 29]. In this study, the rate of *E. faecalis* in AES was 17.6% versus only 1.5% of the isolated bacteria in AA. According to recommendations for perioperative antibiotic therapy, the administration of antibiotics against *Enterococci* is not mandatory because the control of the infectious focus is considered adequate in both AA and AES [30]. In contrast, the selection of vancomycin-resistant *Enterococci* is feared in cases of a widespread empiric therapy of this organism, and a therapeutic failure rate of 28% in patients with isolated *Enterococcus* has been described [6, 31]. Therefore, for surgeons, knowledge about this germ in an intra-abdominal infection is crucial, particularly in cases of MDR in *Enterococci*. In this study, in AA, only one MDR *E. faecalis* was cultivated, whereas in AES, MDR *Enterococci* were more frequently found. In smears in COM peritonitis, MDR *E. faecalis* represented one third (31.5%) of the ESKAPE germs, but only half of them (53.6%) were found in HOS peritonitis.

This study demonstrates that ESKAPE bacteria are important in AA, although these MDR bacteria are rather rarely found in this condition. If the surgeon's knowledge about pathogens in intra-abdominal infections is restricted to the literature or the screening of disease clusters, he might obtain a deficient picture of his opponent. Consequently, one must oppose the criticism of microbiological testing in AA. The germs that are isolated are relevant to the clinical course, and they differ from what is found in other emergency surgeries.

One further argument against microbiological investigations in AA is the time required for bacteria cultivation and AST. Patients may already be discharged before the release of the microbiological results [32]. Indeed, in this study, the majority of the microbiological results were released on or after the date of discharge. However, in each and every case of delayed clinical recovery, failure of convalescence, or readmission, the results of the intraoperative swab could optimize the antibiotic therapy and helped identify multidrug-resistant bacteria. However, the knowledge of the identified bacteria might allow the de-escalation or termination of antibiotic therapy. In at least nine patients (1.5%), the postoperative therapy was altered according to the swab results.

In times of increasing resistance to antibiotic therapy, the choice of PAP antibiotics and of postoperative therapy may be challenging, especially in countries with high antibiotic resistance rates [11]. The detection of epidemiological changes in local resistance patterns within an institution may help select the appropriate antibiotic therapy. Solomkin et al. recommended avoiding agents if resistance to a given antibiotic was present in 10–20% or more of intra-abdominal organisms in the community [6]. By obtaining swabs during AE, additional information about these patterns can be obtained.

Limitations

We are aware of the limitations of this retrospective study: First, the collective is limited, especially with regard to MDR bacteria in AA. Second, the retrospective design of the study and its single-center character restrict its validity.

The retrospective nature of this study and the limited count of patients with altered antibiotic therapy upon receipt of the MDR testing do not enable a conclusion on how this influences the course of these patients.

Nonetheless, our findings are in line with the literature and enlarge the knowledge regarding particular aspects of the topic that have not yet been elucidated.

Conclusion

This study reveals a low rate of complications in AA. The most common complications are infections, namely SSIs. These infectious complications must not be underestimated, and in patients who suffer from SSI, the microbiome and its resistances are of importance. There are differences in the intra-abdominal microbiome in different clusters of emergency surgery. Although virulent germs and MDR bacteria are rather seldom detected in appendicitis, these germs are a distinct factor of morbidity.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest

References

1. Andersen BR, Kallehave FL, Andersen HK (2003) Antibiotics versus placebo for prevention of postoperative infection after appendicectomy. Cochrane Database Syst Rev 2:CD001439. doi:10.1002/14651858.cd001439
2. Fagenholz PJ, Peev MP, Thabet A, Michailidou M, Chang Y, Mueller PR, Hahn PF, Velmahos GC (2015) Abscess due to perforated appendicitis: factors associated with successful percutaneous drainage. Am J Surg. doi:10.1016/j.amjsurg.2015.07.017
3. Garg CP, Vaidya BB, Chengalath MM (2009) Efficacy of laparoscopy in complicated appendicitis. Int J Surg 7(3):250–252. doi:10.1016/j.ijsu.2009.04.007
4. Taguchi Y, Komatsu S, Sakamoto E, Norimizu S, Shingu Y, Hasegawa H (2016) Laparoscopic versus open surgery for complicated appendicitis in adults: a randomized controlled trial. Surg Endosc 30(5):1705–1712. doi:10.1007/s00464-015-4453-x
5. Bodmann KF, und die Expertenkommission der I (2010) Complicated intra-abdominal infections: pathogens, resistance. Recommendations of the Infectliga on antbiotic therapy. Chirurg 81(1):38–49. doi:10.1007/s00104-009-1822-9
6. Solomkin JS, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJ, Baron EJ, O'Neill PJ, Chow AW, Dellinger EP, Eachempati SR, Gorbach S, Hilfiker M, May AK, Nathens AB, Sawyer RG, Bartlett JG (2010) Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Surg Infect 11(1):79–109. doi:10.1089/sur.2009.9930
7. Gorter RR, Eker HH, Gorter-Stam MA, Abis GS, Acharya A, Ankersmit M, Antoniou SA, Arolfo S, Babic B, Boni L, Bruntink M, van Dam DA, Defoort B, Deijen CL, DeLacy FB, Go PM, Harmsen AM, van den Helder RS, Iordache F, Ket JC, Muysoms FE, Ozmen MM, Papoulas M, Rhodes M, Straatman J, Tenhagen M, Turrado V, Vereczkei A, Vilallonga R, Deelder JD, Bonjer J (2016) Diagnosis and management of acute appendicitis. EAES consensus development conference 2015. Surg Endosc. doi:10.1007/s00464-016-5245-7
8. Davies HO, Alkhamesi NA, Dawson PM (2010) Peritoneal fluid culture in appendicitis: review in changing times. Int J Surg 8(6):426–429. doi:10.1016/j.ijsu.2010.06.016
9. Coccolini F, D'Amico G, Sartelli M, Catena F, Montori G, Ceresoli M, Manfredi R, Di Saverio S, Ansaloni L (2016) Antibiotic resistance evaluation and clinical analysis of acute appendicitis; report of 1431 consecutive worldwide patients: a cohort study. Int J Surg 26:6–11. doi:10.1016/j.ijsu.2015.12.063
10. Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB, Scheld M, Spellberg B, Bartlett J (2009) Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. Clin Infect Dis 48(1):1–12. doi:10.1086/595011
11. Dimopoulos G, Kollef MH, Cohen J (2016) In 2035, will all bacteria be multiresistant? Yes Intensive Care Med. doi:10.1007/s00134-016-4310-y

12. Lodise TP, McKinnon PS, Levine DP, Rybak MJ (2007) Impact of empirical-therapy selection on outcomes of intravenous drug users with infective endocarditis caused by methicillin-susceptible Staphylococcus aureus. Antimicrob Agents Chemother 51(10): 3731–3733. doi:10.1128/AAC.00101-07
13. Pletz MW, Eckmann C, Hagel S, Heppner HJ, Huber K, Kämmerer W, Schmitz FJ, Wilke M, Grabein B (2015) Current strategies against multi-drug resistant organisms. Dtsch Med Wochenschr 140(13):975–981. doi:10.1055/s-0041-102452
14. McNamara MJ, Pasquale MD, Evans SR (1993) Acute appendicitis and the use of intraperitoneal cultures. Surg Gynecol Obstet 177(4): 393–397
15. Gladman MA, Knowles CH, Gladman LJ, Payne JG (2004) Intra-operative culture in appendicitis: traditional practice challenged. Ann R Coll Surg Engl 86(3):196–201. doi:10.1308/003588404323043346
16. Kokoska ER, Silen ML, Tracy TF Jr, Dillon PA, Kennedy DJ, Cradock TV, Weber TR (1999) The impact of intraoperative culture on treatment and outcome in children with perforated appendicitis. J Pediatr Surg 34(5):749–753
17. Lob SH, Badal RE, Bouchillon SK, Hawser SP, Hackel MA, Hoban DJ (2013) Epidemiology and susceptibility of Gram-negative appendicitis pathogens: SMART 2008-2010. Surg Infect 14(2):203–208. doi:10.1089/sur.2012.034
18. Delgado-Rodriguez M, Sillero-Arenas M, Medina-Cuadros M, Martinez-Gallego G (1997) Nosocomial infections in surgical patients: comparison of two measures of intrinsic patient risk. Infect Control Hosp Epidemiol 18(1):19–23
19. Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40(5):373–383
20. Linder MM, Wacha H, Feldmann U, Wesch G, Streifensand RA, Gundlach E (1987) The Mannheim peritonitis index. An instrument for the intraoperative prognosis of peritonitis. Chirurg 58(2):84–92
21. Bhangu A, Soreide K, Di Saverio S, Assarsson JH, Drake FT (2015) Acute appendicitis: modern understanding of pathogenesis, diagnosis, and management. Lancet 386(10000):1278–1287. doi:10.1016/S0140-6736(15)00275-5
22. Foo FJ, Beckingham IJ, Ahmed I (2008) Intra-operative culture swabs in acute appendicitis: a waste of resources. Surgeon 6(5): 278–281
23. Sartelli M, Weber DG, Ruppé E, Bassetti M, Wright BJ, Ansaloni L, Catena F, Coccolini F, Abu-Zidan FM, Coimbra R, Moore EE, Moore FA, Maier RV, De Waele JJ, Kirkpatrick AW, Griffiths EA, Eckmann C, Brink AJ, Mazuski JE, May AK, Sawyer RG, Mertz D, Montravers P, Kumar A, Roberts JA, Vincent JL, Watkins RR, Lowman W, Spellberg B, Abbott IJ, Adesunkanmi AK, Al-Dahir S, Al-Hasan MN, Agresta F, Althani AA, Ansari S, Ansumana R, Augustin G, Bala M, Balogh ZJ, Baraket O, Bhangu A, Beltrán MA, Bernhard M, Biffl WL, Boermeester MA, Brecher SM, Cherry-Bukowiec JR, Buyne OR, Cainzos MA, Cairns KA, Camacho-Ortiz A, Chandy SJ, Che Jusoh A, Chichom-Mefire A, Colijn C, Corcione F, Cui Y, Curcio D, Delibegovic S, Demetrashvili Z, De Simone B, Dhingra S, Diaz JJ, Di Carlo I, Dillip A, Di Saverio S, Doyle MP, Dorj G, Dogjani A, Dupont H, Eachempati SR, Enani MA, Egiev VN, Elmangory MM, Ferrada P, Fitchett JR, Fraga GP, Guessennd N, Giamarellou H, Ghnnam W, Gkiokas G, Goldberg SR, Gomes CA, Gomi H, Guzmán-Blanco M, Haque M, Hansen S, Hecker A, Heizmann WR, Herzog T, Hodonou AM, Hong SK, Kafka-Ritsch R, Kaplan LJ, Kapoor G, Karamarkovic A, Kees MG, Kenig J, Kiguba R, Kim PK, Kluger Y, Khokha V, Koike K, Kok KY, Kong V, Knox MC, Inaba K, Isik A, Iskandar K, Ivatury RR, Labbate M, Labricciosa FM, Laterre PF, Latifi R, Lee JG, Lee YR, Leone M, Leppaniemi A, Li Y, Liang SY, Loho T, Maegele M, Malama S, Marei HE, Martin-Loeches I, Marwah S, Massele A, McFarlane M, Melo RB, Negoi I, Nicolau DP, Nord CE, Ofori-Asenso R, Omari AH, Ordonez CA, Ouadii M, Pereira Júnior GA, Piazza D, Pupelis G, Rawson TM, Rems M, Rizoli S, Rocha C, Sakakhushev B, Sanchez-Garcia M, Sato N, Segovia Lohse HA, Sganga G, Siribumrungwong B, Shelat VG, Soreide K, Soto R, Talving P, Tilsed JV, Timsit JF, Trueba G, Trung NT, Ulrych J, van Goor H, Vereczkei A, Vohra RS, Wani I, Uhl W, Xiao Y, Yuan KC, Zachariah SK, Zahar JR, Zakrison TL, Corcione A, Melotti RM, Viscoli C, Viale P (2016) Antimicrobials: a global alliance for optimizing their rational use in intra-abdominal infections (AGORA). World J Emerg Surg 11:33. doi:10.1186/s13017-016-0089-y
24. Bayhan G, Tanır G, Karaman I, Ozkan S (2013) Comamonas testosteroni: an unusual bacteria associated with acute appendicitis. Balkan Med J 30(4):447–448. doi:10.5152/balkanmedj.2013.9135
25. Gul M, Ciragil P, Bulbuloglu E, Aral M, Alkis S, Ezberci F (2007) Comamonas testosteroni bacteremia in a patient with perforated acute appendicitis. Short communication. Acta Microbiol Immunol Hung 54(3):317–321. doi:10.1556/AMicr.54.2007.3.6
26. Lob SH, Badal RE, Hackel MA, Sahm DF (2016) Epidemiology and antimicrobial susceptibility of Gram-negative pathogens causing intra-abdominal infections in pediatric patients in Europe-SMART 2011-2014. J Pediatric Infect Dis Soc. doi:10.1093/jpids/piv109
27. Mazuski JE (2007) Antimicrobial treatment for intra-abdominal infections. Expert Opin Pharmacother 8(17):2933–2945. doi:10.1517/14656566.8.17.2933
28. Dworniczek E, Piwowarczyk J, Bania J, Kowalska-Krochmal B, Walecka E, Seniuk A, Dolna I, Gosciniak G (2012) Enterococcus in wound infections: virulence and antimicrobial resistance. Acta Microbiol Immunol Hung 59(2):263–269. doi:10.1556/AMicr.59.2012.2.11
29. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR (1999) Guideline for Prevention of Surgical Site Infection, 1999. Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices Advisory Committee. Am J Infect Control 27(2):97–132 quiz 133-134; discussion 196
30. Harbarth S, Uckay I (2004) Are there patients with peritonitis who require empiric therapy for Enterococcus? Eur J Clin Microbiol Infect Dis 23(2):73–77. doi:10.1007/s10096-003-1078-0
31. Burnett RJ, Haverstock DC, Dellinger EP, Reinhart HH, Bohnen JM, Rotstein OD, Vogel SB, Solomkin JS (1995) Definition of the role of Enterococcus in intraabdominal infection: analysis of a prospective randomized trial. Surgery 118(4):716–721 discussion 721-713
32. Moawad MR, Dasmohapatra S, Justin T, Keeling N (2006) Value of intraoperative abdominal cavity culture in appendicectomy: a retrospective study. Int J Clin Pract 60(12):1588–1590. doi:10.1111/j.1742-1241.2005.00774.x

Langenbeck's Archives of Surgery
https://doi.org/10.1007/s00423-019-01777-y

ORIGINAL ARTICLE

Antibiotic-treated acute appendicitis—reception in social media

Alexander Reinisch[1] · Stefan Robert Schröder[1] · Frank Ulrich[1] · Winfried Padberg[2] · Juliane Liese[2]

Received: 19 December 2018 / Accepted: 13 March 2019

Abstract

Purpose Social media, especially Twitter®, is becoming increasingly important for medical topics. Systematic analyses of the content of these tweets are rare. To date, no analysis of the reception of antibiotic/non-operative-treated acute appendicitis on Twitter® has been performed.

Methods Tweets with the content "appendicitis," "appendix," and "appendectomy" from December 31, 2010, to September 27, 2017, were recorded. Further analysis was performed by secondary search strings related to antibiotic-treated acute appendicitis. Subsequent systematic analysis of content, author groups, and followers was performed.

Results Out of 22,962 analyzed tweets, 3400 were applicable on all search strings, and 349 dealt meaningfully with antibiotic-treated acute appendicitis. 47.9% of the tweets were published by individuals, of which non-surgical consultants comprised the largest group. The tweets published by organizations and institutions were mostly published by publishing platforms. Half of the tweets were neutral, with an overall positive trend for antibiotic-treated acute appendicitis, but significant differences were noted among the authors. The number of followers showed a wide range, with an considerable numeric impact.

Conclusion The scientific discussion of antibiotic-treated acute appendicitis is reflected on Twitter®. Overall, antibiotic-treated acute appendicitis is presented in a neutral and differentiated manner on Twitter®, but this picture is exclusively derived from assessment of a variety of tweets. Individual tweets are partially undifferentiated in content and misrepresent antibiotic-treated acute appendicitis. In addition, content and intentions are significantly author dependent. Scientists should therefore use Twitter® to make sound medical information heard. If this policy is not implemented, the importance of inadequate and incorrect information transfer is indirectly increased.

Keywords Appendicitis · Antibiotics · Social media · Twitter®

Introduction

Social media is increasingly important for the formation of opinion on medical topics. To date, communication on medical topics is primarily based on professional medical publication platforms and congresses. Healthcare information published in medical journals, congresses, or internet platforms, such as Medscape.com and WebMD.com, is mostly of limited value to medical non-professionals if not strictly restricted to healthcare professionals. Medical non-professionals obtain information regarding upcoming or changing medical topics typically from the non-specialized media, television or newspapers. Although information on latest scientific and medical topics may be technically accessible for medical non-professionals, the pricing and the complexity of presentation, especially in medical journals, results in an information imbalance to the disadvantage of non-healthcare-professionals. Nevertheless, most patients are not educated, trained, or active in the medical field, and the informed patient is searching information about their own disease, diagnostic options and treatments online.

This gap is filled by social media. Main advantages of gathering medical information on social media are the low-threshold access, the often easy-to-understand presentations, and the immediate dissemination of information. The presentation of medical data on professional platforms is complex, while information on social media platforms is comparatively condensed. Twitter® restricts postings to 280 (140 until November 2017) characters. To spread healthcare

✉ Alexander Reinisch
alexander_reinisch@hotmail.com

[1] Department of General, Visceral and Oncologic Surgery, Hospital and Clinics Wetzlar, Forsthausstr. 1, 35578 Wetzlar, Germany

[2] Department of General, Visceral, Thoracic, Transplant and Pediatric Surgery, University Hospital Giessen, Giessen, Germany

Published online: 29 March 2019

information, microblogging via Twitter® is the most popular form [1]. Initial studies show that Twitter® is being used by various interest groups and organizations for the targeted dissemination of medical information or to analyze public reception on medical topics [2, 3]. Thus, the analysis of content and goals of these tweets is of great interest.

While professional medical publication systems mostly offer a system of revision and control, social media regularly lacks any control. Moreover, there is very little information regarding who is posting what type of information. While this information is lacking, the effect of Twitter® on public discourse becomes evident and is lately being realized by medical professionals [4]. The aim of this study was to examine the dissemination of healthcare information via Twitter® on a specialized medical topic that is of great public interest. Acute appendicitis is a well-known and frequent disease with a vast number of affected people. Alternative therapies are therefore of great interest, especially non-operative antibiotic-based therapy of acute appendicitis.

Appendicitis and the operative removal of the appendix are broadly known among non-healthcare-professionals. Therefore, the reception of the relatively new and not-yet-conclusive therapy without surgery is of great interest. This interest has also arisen because the scientific discussion of this therapeutic concept is by no means complete [5–7].

Material and methods

Twitter® has been available since March 21, 2006. All microblogs ("tweets") containing the words "appendicitis," "appendectomy," and "appendix" (primary search strings) posted between the launch of Twitter® and September 27, 2017, were extracted. The latter date was selected because of major changes in Twitter's® terms of use. Non-medically related and double-tweets were excluded as well as those only describing the personal course of the disease (individual content) or reporting on celebrities. The content of remaining tweets was further analyzed for the secondary search string ("antibiotics," "antibiotic," and "drugs"). Picture posts were analyzed, as some contained presentations or diagrams matching the criteria of interest. The content analysis followed the approach described by Holsti and Berelson for communication research [8, 9].

The third step was a detailed analysis of the tweets matching primary and secondary search strings. All tweets addressing non-operative, antibiotic treatment of acute appendicitis were classified according to the date of publication, author, source, and content. The classification of the sources distinguished as medical non-professionals vs. professionals. The later were subdivided in individual tweets and organizational tweets. Individual tweets were published by consultants for surgery (surgeons), consultants not active in surgery (non-surgery consultants), general practitioners, and other medical professionals. Organizational tweets were published by hospitals/governmental organizations, enterprises and non-governmental organization, or publication platforms (e.g., online platforms of publishing houses or media companies) and news agencies.

The monthly number of tweets published on antibiotic-treated acute appendicitis was analyzed. Noticeable peaks in tweet numbers were correlated with the publication of manuscripts on the topic, as determined by a *PubMed* search (search strings "antibiotic," "antibiotics," "appendicitis," and "surgery" in the timeframe of the peak ± 1 month).

Content classification was conducted by analysis of all tweets by the authors (AR, JL) individually, and classification was compared. Inconsistently classified tweets were submitted to another author (SSR). A two-out-of-three vote was used for classification. If this vote could not be achieved, the tweet was excluded. Content classification criteria were as follows:

- *Unfairly positive*—antibiotic-treated acute appendicitis as the only or superior therapeutic option. Concealment of possible negative side effects
- *A positive option*—antibiotic-treated acute appendicitis as a therapeutic option that may have advantages compared with operative therapy. Emphasized the pros of this non-operative therapy
- *Neutral*—introduction of antibiotic-treated acute appendicitis as a therapeutic option without judgment. Equal presentation of pros and cons
- *A negative option*—antibiotic-treated acute appendicitis as a therapeutic option. Underlining the superiority of surgical treatment and the cons
- *Unfairly negative*—antibiotic-treated acute appendicitis as a careless, negligent or widely ineffective therapeutic option

Fisher's exact test was used to analyze the differences in the categorical variables for predicted values < 5; otherwise, the two-sided chi-square test was used. Unless otherwise stated, all tests were two-tailed, and p values < 0.05 were considered significant. All data analyses were performed using SPSS, version 24 (IBM, Armonk, USA).

Results

Between the launch of Twitter® and December 31, 2010, 443 tweets contained the primary search strings. Of these, none matched the secondary search string. Further analysis was restricted to January 1, 2011, to September 27, 2017.

Between January 1, 2011, and September 27, 2017, a total of 22,962 tweets containing "appendicitis," "appendectomy," or "appendix" were analyzed. A total of 3400 of these tweets matched the inclusion criteria and were analyzed for the secondary search strings. The percentage of serious medically related tweets ranged from 9.5% ("appendix") to 38% ("appendectomy"). The primary reason for exclusion was individual content (65%). We were able to identify 364 tweets addressing antibiotic, non-operative therapy of acute appendicitis. In further analysis, 15 tweets were excluded for deficient author information, nonsense content, repetition, or inconsistent classification vote.

Timeline

Viewing the number tweets published per year did not provide a definite conclusion. The maximum number of tweets was published in 2015—134. In 2013, a notable drop was recorded with just four evaluable tweets (Fig. 1).

We noticed distinct peaks in tweet publication on antibiotic-treated acute appendicitis. The *PubMed* search revealed that prior to each peak, a manuscript on non-operative antibiotic treatment of acute appendicitis was published in a highly reputed medical journal (Fig. 1). The evaluation of the therapeutic approach in the identified papers ranged from negative to positive.

The papers that triggered an increase in tweets were published in high-level medical journals (impact factor 5.7–44). However, not every publication on antibiotic-treated acute appendicitis in a high-profile medical journal led to a noticeable increase in tweets [10–12]. In particular, the much-noticed manuscript on the *Non Operative Treatment for Acute Appendicitis* (*NOTA*) study by Di Saverio et al. (*Annals of Surgery*) in 2014 triggered no significant increase [13].

Source analysis

In total, 167 tweets were posted by individuals. Of these, 109 were posted by medical professionals, and 58 were posted by non-medical lay people (individuals without formalized medical education; hereinafter: "medical non-professionals"). A total of 182 tweets were posted by organizations, and the majority of 118 tweets were posted by publication platforms.

Of the 109 medical professional individuals, 26 (24%) identified themselves as surgeons, and 48 (44%) were nonsurgical consultants. Furthermore, 9 individuals claimed to be general practitioners (8% of medical professional individuals), leaving 24% ($n = 26$) as otherwise classified medical professionals.

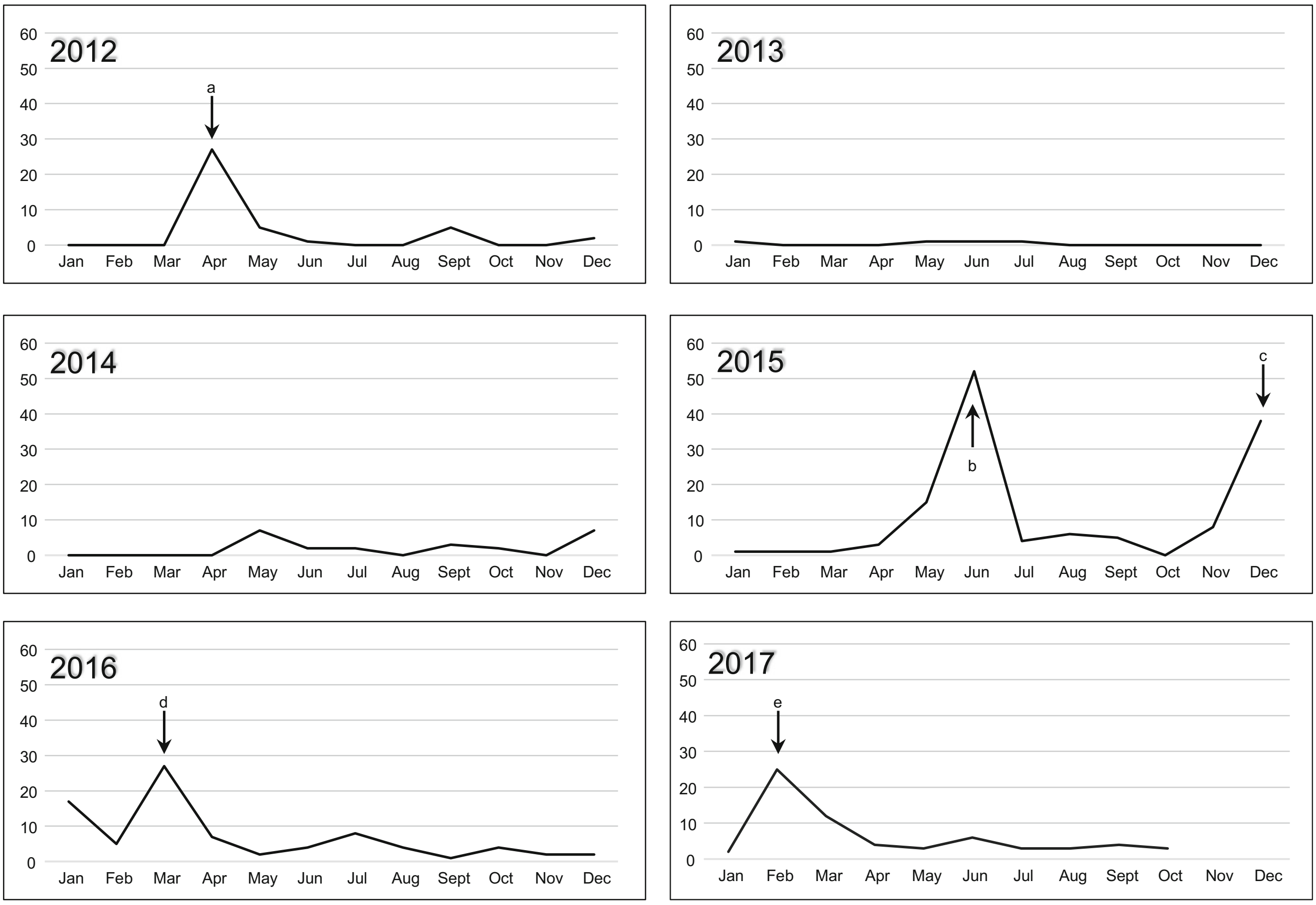

Fig. 1 Time-dependent presentation of the tweet number and publications in *PubMed*. (a) Varadhan et al., *BMJ* [10]. (b) Salminen et al., *JAMA* [11]. (c) Minneci et al., *JAMA Surg* (Epub) [12]. (d) Sallinen et al., *BJS* (Epub) [7]. (e) Georgiou et al., *Pediatrics* [21]

A total of 16.6% of all tweets were published by non-healthcare-professionals.

Among 182 tweets published by organizations, 118 (65%) were issued by publishing platforms. The remaining tweets were posted in similar proportions by enterprises or non-governmental organization ($n = 33$; 18%) and hospitals or governmental organization ($n = 31$; 17%). The relations outlined above did not change during the observation period.

Content analysis

The content of approximately half of the tweets were classified as *neutral* ($n = 178$; 51%). Forty-one (12%) tweets were *unfairly positive* tweets compared with only 1 *unfairly negative* tweet (0.3%).

The relationship of *a positive option* versus *a negative option* tweets was clearly in favor of *a positive option* tweets. In total, 29% of all tweets were *a positive option* tweets ($n = 102$), which is approximately four times more than *a negative option* tweet ($n = 27$; 8%). In summary, 41% of all tweets on antibiotic-treated acute appendicitis were in favor of this therapeutic concept.

Source-content correlation

In the general study cohort, as well as in each subanalysis, most tweets had a neutral content. However, there were noticeable differences between tweets by individuals and organizations as well as in each of these groups.

Comparing medical professionals and non-professionals, we observed a slight tendency towards *a positive option* tweets for non-professionals ($p = 0.23$).

We observed a tendency towards fewer *unfairly positive* tweets by non-surgical consultants that reached significance compared with the individuals ($p = 0.09$ vs. $p = 0.02$). Only 4% of the tweets by non-surgical consultants were *unfairly positive*, while 8% of the tweets by surgeons and 22% (2 of 9) tweets from general practitioners were *unfairly positive*. Interestingly, 26% of the tweets by medical non-professionals were *unfairly positive*, which is significantly more than tweets by other individuals and the general study population ($p = 0.002$ vs. $p = 0.001$). There was no difference in the rate of *unfairly positive* tweets between medical professionals and surgeons.

Furthermore, non-professionals posted significantly fewer *a negative option* tweets compared with other individuals ($p = 0.02$) but not in comparison with the general population ($p = 0.27$).

A total of 3% of the tweets posted by hospitals or governmental organizations were *unfairly positive*; this is the lowest rate among organizational tweets (enterprises/non-governmental organizations 18%, publication platforms 9%).

Surgeons published significantly more negative and significantly fewer positive tweets compared with other individuals (*a negative option*, $p < 0.0001$; *a positive option*, $p = 0.01$) or the general study population (*a negative option*, $p < 0.0001$; *a positive option*, $p < 0.0001$). We observed a strong tendency towards positive tweets in the non-surgery consultants group ($p = 0.058$). This observation evens out if the non-surgery consultants are compared with the remaining individuals ($p = 0.29$). Tweets published by individuals represented significantly more often *a positive option* ($p = 0.02$) or *a negative option* ($p = 0.02$) than tweets released by organizations.

A noticeably low rate of *a negative option* tweets was posted by publication platforms (3%), and this rate was significantly less than the remainder of the study population (10%, $p = 0.01$). The overall analysis showed that most tweets on antibiotic-treated acute appendicitis were *neutral*. However, on the whole, there was a tendency towards a positive image, but this exhibited noticeable differences between the groups of authors (Table 1).

Impact analysis

The number of followers of tweets on antibiotic-treated acute appendicitis ranged from 9 to 393,000. The mean number of followers did not differ significantly among the publishers of *unfairly positive*/*a positive option*, *neutral,* or *unfairly negative*/*a negative option* tweets and ranged from 10,061 (*a positive option*, SD ± 22,853) to 11,871 (*unfairly positive*; SD ± 61,080). The mean number of followers of organizational tweets was significantly higher than that of individuals ($13{,}010 \pm 29{,}565$ vs. 1468 ± 345, $p < 0.0001$); > 100,000 followers on antibiotic-treated acute appendicitis tweets were reached exclusively by hospitals/governmental organizations and publication platforms.

A total of 105 (30%) tweets were "liked," ranging from 1 to 119 "likes" (median 4.0/SD ± 11.9).

Ninety-two (26%) tweets were re-tweeted, ranging from 1 to 119 times (median 4.8, SD ± 13.7). All re-tweeted tweets were also "liked." The mean number of "likes" per tweet ranged from 1.25 (*unfairly positive*; SD ± 0.4) to 5.0 (*neutral*; SD ± 15.0); however, no significant differences were noted between the groups.

The count of "likes" was significantly higher among *neutral* tweets compared with all other groups ($p < 0.0001$). Interestingly, significantly more readers "liked" *a positive option* tweets than *a negative option* tweets ($p < 0.0001$).

The latter findings were similar to the analysis of the re-tweets. The only difference was found in a lower degree of significance between *a positive option* and *neutral* tweets ($p = 0.04$).

Table 1 Distribution of the content evaluation by author groups (%)

		unfairly positive		a positive option		neutral		a positive option		unfairly negative	
Individuals	Non-professionals	26		42		29		3		0	
		4	9	7	14	5	10	1	1	0	0
	General practitioners	22		44		11		11		11	
		1	1	1	2	0	1	0	1	0	1
	Medical professionals; other	8		35		50		8		0	
		1	1	3	5	4	8	1	1	0	0
	Consultants, non-surgery	4		42		44		10		0	
		1	1	6	12	6	13	1	3	0	0
	Surgeons	8		8		50		35		0	
		1	1	1	1	4	8	3	5	0	0
	Individuals (cumulative)	8	13	18	34	19	40	6	11	0	1
Organizations	Enterprises, non-governmental organization	18		27		45		9		0	
		2	3	2	5	4	8	1	2	0	0
	Hospitals, governmental/public organizations	3		23		68		6		0	
		0	1	2	4	6	12	1	1	0	0
	Publication platform and news agency	9		23		65		3		0	
		3	6	8	15	22	42	1	2	0	0
	Organizations (cumulative)	5	10	12	24	32	62	3	5	0	0

Legend	[%] of Group	
	[%] of all	[%] of subgroup

0-9.9	10-19.9	20-29.9	30-39.9	40-49.9	50-59.9	60-69.9

Discussion

Our work is among the first comprehensive analyses of the discussion of a current broad-based medical topic in a social medium. Until recently, social media played a subordinate role in medical research. However, the importance of social media for medical research is also becoming increasingly obvious [14].

Social media is used both to generate primary data on diseases and to examine the benefits of social media for the dissemination of medical information [15–17]. For the latter purpose, Twitter® is the most important social medium besides Facebook. Thus, the number of studies dealing with social media in the medical context quintupled in the years 2016 and 2017 compared with that of 2010. Our investigations reflect the following: Tweets dealing with antibiotic-treated acute appendicitis could be observed to a significant extent from 2012 onwards. The total number of these tweets in 2015, 2016, and 2017 was significantly higher than that in previous years.

The proportion of tweets about antibiotic-treated acute appendicitis with useful content was between 9.5 and 38% in our study. These values are comparable to the observations of Chandrasekaran et al., who identified 39% of the tweets examined as "not useful" and 14% as "misleading" [16].

The number of followers of tweets regarding antibiotic-treated acute appendicitis however is remarkable. Tweets about non-operative, antibiotic-treated acute appendicitis reached a median of greater than 10,000 followers. This number is interesting compared with the readership of scientific journals. Data on this issue are scarce, but even the most highly rated surgical journals, such as *Annals of Surgery*, report only approximately 2500 subscribers and 50,000 monthly site visits [18]. Other well-known surgical journals report 800–2200 downloads per article [19]. Therefore, this analysis proves that medical tweets have a notable reach of readers compared with the specialist press. Most readers, up to greater than 100,000, are reached by tweets from professional publishing platforms. The content neutrality of these platforms cannot be assumed, and tweets should be critically questioned and announced.

Our research also shows that social media reflects publications in medical journals. We observed peaks in the number of tweets following publications on this topic in high-level journals. However, we identified only four evaluable tweets in 2013 possibly because only the announcement of a prospective study on the antibiotic-treated acute appendicitis was noticeable in this year [20].

Our study shows that the current controversy is reflected in social media [6, 7]. Meta-analyses and randomized controlled trials tend to be to the detriment of antibiotic-treated acute appendicitis [5]. However, there are also articles that reported very positively on this treatment [21, 22]. The content spectrum of the tweets ranged from *unfairly positive* to *unfairly negative* with a maximum of *neutral* tweets. Overall, we observed a tendency towards positive tweets. Articles in medical journals reported predominantly neutral points of view on antibiotic-treated acute appendicitis; however, to a large extent, they stressed the disadvantages/risks of non-surgical therapy. The crucial difference between medical publications and tweets is that the latter usually report unilaterally. The controversy of the discussion is therefore only revealed by the overall view of numerous tweets.

We observed significant differences in the rating of non-operative therapy of acute appendicitis with antibiotics by different groups of authors. These differences were found between groups of medically professionals, between medical professionals and non-professionals, as well as between individuals and organizations. Such differentiations cannot be made when looking at articles in medical journals. Fung et al. performed an analysis of various tweets authored by different groups on "Global Health" in 2014–2015. Its results were comparable to ours [2].

In a study by Hanson et al., the percentage of patients who chose a non-operative, antibiotic treatment for acute appendicitis for themselves or their child was less than 15% [23]. This finding is in contrast to our observation of a rather positive reception of antibiotic-treated acute appendicitis, especially among medical non-professionals. We suspect that this reflects the ambivalence regarding the respect for surgery or anesthesia versus the fear of complications caused by delayed surgery. This finding would be consistent with the results of the survey by O'Connell et al. [24]. While our study also proved that medical non-professionals were more positive regarding antibiotic-treated acute appendicitis, the survey by Althans et al. showed a different picture. In that study, only 24.3% of medical students would want antibiotic treatment for appendicitis for themselves [25].

Our study showed that medical topics are reflected in the social media in a broad and timely manner. The discussion in social media is led by a range of authors, going far beyond what has thus far shaped the scientific discussion. Even though our study provided little information about the recipients of the tweets, it must be assumed that the readership is much wider than that of medical journals. Our study showed that the lack of a review process in social media also gives rise to the publication of inadequate, useless and harmful information. This finding emphasizes the necessity for medical specialists to publish their findings in social media, as this is the only method to provide the public with evidence-based information on this channel. Abandoning this task would increase the importance of interest-guided or completely unscientific tweets.

There are distinct limitations to this study. There is a possibility of duplicate or fake accounts or wrong authors' statements regarding their profession. The study was only a snapshot of the rapidly changing opinions in social media. Compared with analysis on medical topics that are more interesting to the general public, especially drug abuse or plastic surgery, the number of tweets analyzed is rather lower [3, 26].

In this context, further studies are necessary, i.e., the targeted analysis of the recipients of publication in social media.

Conclusion

The scientific and non-scientific discussion of antibiotic therapy of acute appendicitis is reflected on Twitter®. The Twitter® discussion of this therapeutic option for acute appendicitis reaches a large readership compared with medical journals and is influenced by scientific publications. The presentation of this treatment option varies significantly between different groups of authors and is presented in a manner intending to promote a one-sided point of view that is not a fair discussion of the pros and cons.

Only by observing a large number of utterances does a differentiated picture emerge of the topic.

Authors' contributions Study conception and design—A. Reinisch and J. Liese. Drafting of the manuscript—A. Reinisch and J. Liese. Acquisition of data—A. Reinisch and S.R. Schröder. Analysis and interpretation of data—A. Reinisch, S.R. Schröder, and J. Liese. Critical revision of the manuscripts—J. Liese, F. Ulrich, and W. Padberg. Final approval of the version to be submitted—all authors.

Compliance with ethical standards

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors. This study was not funded.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Bartlett C, Wurtz R (2015) Twitter and public health. J Public Health Manag Pract 21(4):375–383. https://doi.org/10.1097/PHH.0000000000000041
2. Fung IC, Jackson AM, Ahweyevu JO, Grizzle JH, Yin J, Tse ZTH, Liang H, Sekandi JN, Fu KW (2017) #Globalhealth twitter conversations on #malaria, #HIV, #TB, #NCDS, and #NTDS: a cross-sectional analysis. Ann Glob Health 83(3–4):682–690. https://doi.org/10.1016/j.aogh.2017.09.006
3. Kalandar A, Al-Youha S, Al-Halabi B, Williams J (2018) What does the public think? Examining plastic surgery perceptions through the Twitterverse. Plast Reconstr Surg 142(1):265–274. https://doi.org/10.1097/PRS.0000000000004484
4. Nawa N, Ishida H, Suginobe H, Katsuragi S, Baden H, Takahashi K, Narita J, Kogaki S, Ozono K (2018) Analysis of public discourse on heart transplantation in Japan using social network service data. Am J Transplant 18(1):232–237. https://doi.org/10.1111/ajt.14527
5. Harnoss JC, Zelienka I, Probst P, Grummich K, Müller-Lantzsch C, Harnoss JM, Ulrich A, Büchler MW, Diener MK (2017) Antibiotics versus surgical therapy for uncomplicated appendicitis: systematic review and meta-analysis of controlled trials (PROSPERO 2015: CRD42015016882). Ann Surg 265(5):889–900. https://doi.org/10.1097/SLA.0000000000002039
6. Podda M, Cillara N, Di Saverio S, Lai A, Feroci F, Luridiana G, Agresta F, Vettoretto N, Appendicitis AISoHSSGoA (2017) Antibiotics-first strategy for uncomplicated acute appendicitis in adults is associated with increased rates of peritonitis at surgery. A systematic review with meta-analysis of randomized controlled trials comparing appendectomy and non-operative management with

antibiotics. Surgeon 15(5):303–314. https://doi.org/10.1016/j.surge.2017.02.001
7. Sallinen V, Akl EA, You JJ, Agarwal A, Shoucair S, Vandvik PO, Agoritsas T, Heels-Ansdell D, Guyatt GH, Tikkinen KA (2016) Meta-analysis of antibiotics versus appendicectomy for non-perforated acute appendicitis. Br J Surg 103(6):656–667. https://doi.org/10.1002/bjs.10147
8. Berelson B (1952) Content analysis in communcation research. Free Press, Glencoe
9. Holsti OR (1969) Analysis for the social sciences and humanities. Addison-Wesley, Reading
10. Varadhan KK, Neal KR, Lobo DN (2012) Safety and efficacy of antibiotics compared with appendicectomy for treatment of uncomplicated acute appendicitis: meta-analysis of randomised controlled trials. BMJ 344:e2156
11. Salminen P, Paajanen H, Rautio T, Nordström P, Aarnio M, Rantanen T, Tuominen R, Hurme S, Virtanen J, Mecklin JP, Sand J, Jartti A, Rinta-Kiikka I, Grönroos JM (2015) Antibiotic therapy vs appendectomy for treatment of uncomplicated acute appendicitis: the APPAC randomized clinical trial. JAMA 313(23):2340–2348. https://doi.org/10.1001/jama.2015.6154
12. Minneci PC, Mahida JB, Lodwick DL, Sulkowski JP, Nacion KM, Cooper JN, Ambeba EJ, Moss RL, Deans KJ (2016) Effectiveness of patient choice in nonoperative vs surgical management of pediatric uncomplicated acute appendicitis. JAMA Surg 151(5):408–415. https://doi.org/10.1001/jamasurg.2015.4534
13. Di Saverio S, Sibilio A, Giorgini E, Biscardi A, Villani S, Coccolini F, Smerieri N, Pisano M, Ansaloni L, Sartelli M, Catena F, Tugnoli G (2014) The NOTA Study (Non Operative Treatment for Acute Appendicitis): prospective study on the efficacy and safety of antibiotics (amoxicillin and clavulanic acid) for treating patients with right lower quadrant abdominal pain and long-term follow-up of conservatively treated suspected appendicitis. Ann Surg 260(1):109–117. https://doi.org/10.1097/sla.0000000000000560
14. Househ M, Borycki E, Kushniruk A (2014) Empowering patients through social media: the benefits and challenges. Health Informatics J 20(1):50–58. https://doi.org/10.1177/1460458213476969
15. Chen X, Deldossi M, Aboukhamis R, Faviez C, Dahamna B, Karapetiantz P, Guenegou-Arnoux A, Girardeau Y, Guillemin-Lanne S, Lillo-Le-Louët A, Texier N, Burgun A, Katsahian S (2017) Mining adverse drug reactions in social media with named entity recognition and semantic methods. Stud Health Technol Inform 245:322–326
16. Chandrasekaran N, Gressick K, Singh V, Kwal J, Cap N, Koru-Sengul T, Curry CL (2017) The utility of social media in providing information on Zika virus. Cureus 9(10):e1792. https://doi.org/10.7759/cureus.1792
17. Lachmar EM, Wittenborn AK, Bogen KW, McCauley HL (2017) #MyDepressionLooksLike: examining public discourse about depression on twitter. JMIR Ment Health 4(4):e43. https://doi.org/10.2196/mental.8141
18. Wolters Kluwer (2018) Media kit annals of surgery. Wolters Kluwer. http://advertising.lww.com/media-kits/annals-surgery.html. Accessed June 6th 2018
19. Springer (2018) Media kit Springer. Springer. https://www.springer.com/medicine/surgery/journal/11605?wt_mc=Other.Other.8.CON546.JS_surg_11605&utm_medium=other&utm_source=other&utm_content=10122017&utm_campaign=8_vmeyer_js_surg_11605. Accessed June 6th 2018
20. Paajanen H, Grönroos JM, Rautio T, Nordström P, Aarnio M, Rantanen T, Hurme S, Dean K, Jartti A, Mecklin JP, Sand J, Salminen P (2013) A prospective randomized controlled multicenter trial comparing antibiotic therapy with appendectomy in the treatment of uncomplicated acute appendicitis (APPAC trial). BMC Surg 13:3. https://doi.org/10.1186/1471-2482-13-3
21. Georgiou R, Eaton S, Stanton MP, Pierro A, Hall NJ (2017) Efficacy and safety of nonoperative treatment for acute appendicitis: a meta-analysis. Pediatrics 139(3):e20163003. https://doi.org/10.1542/peds.2016-3003
22. Park HC, Kim MJ, Lee BH (2017) Randomized clinical trial of antibiotic therapy for uncomplicated appendicitis. Br J Surg 104(13):1785–1790. https://doi.org/10.1002/bjs.10660
23. Hanson AL, Crosby RD, Basson MD (2018) Patient preferences for surgery or antibiotics for the treatment of acute appendicitis. JAMA Surg 153(5):471–478. https://doi.org/10.1001/jamasurg.2017.5310
24. O'Connell EP, White A, Cromwell P, Carroll E, Khan W, Waldron R, Khan IZ, Barry K (2018) Non-operative treatment of appendicitis: public perception and decision-making. Ir J Med Sci 187:1029–1038. https://doi.org/10.1007/s11845-018-1758-5
25. Althans AR, Tamer P, Brady JT, Steinhagen E, Ho VP (2017) Surgery versus antibiotics for uncomplicated appendicitis: which would a medical student want? Surg Infect 18(8):868–873. https://doi.org/10.1089/sur.2017.129
26. Allem JP, Dharmapuri L, Unger JB, Cruz TB (2018) Characterizing JUUL-related posts on twitter. Drug Alcohol Depend 190:1–5. https://doi.org/10.1016/j.drugalcdep.2018.05.018

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Visceral Medicine

Research Article

Visc Med
DOI: 10.1159/000506058

Received: August 12, 2019
Accepted: January 14, 2020
Published online: February 11, 2020

Nonoperative Antibiotic Treatment of Appendicitis in Adults: A Survey among Clinically Active Surgeons

Alexander Reinisch[a] Martin Reichert[b] Andreas Hecker[b] Winfried Padberg[b]
Frank Ulrich[a] Juliane Liese[b]

[a]Department of General, Visceral and Oncologic Surgery, Hospital and Clinics Wetzlar, Wetzlar, Germany;
[b]Department of General, Visceral, Thoracic, Transplant and Pediatric Surgery, University Hospital of Giessen, Giessen, Germany

Keywords
Appendicitis · Antibiotics · Nonoperative treatment

Abstract
Background: As a result of well-publicized studies, the nonsurgical antibiotic therapy of uncomplicated acute appendicitis has been propagated since 2006. A final assessment regarding efficiency and long-term results is not possible; however, nonoperative therapy of acute appendicitis is actually being discussed more diversely and receives a lot of attention. It is still unknown how far this therapy has found its way into everyday clinical care. ***Methods:*** An online questionnaire was sent to 1,400 randomly selected specialists for general/visceral surgery in Germany. Representativeness was achieved by a preselection according to the geographical origin and the care level of the hospitals. ***Results:*** 14% of surgeons stated that they methodically treat appendicitis conservatively. 38.1% do so in exceptional cases, while 48.8% reject this therapy. For methodically use, sonography or computed tomography is demanded beforehand. Nonoperative therapy is performed more often in metropolitan areas and maximum-care/university hospitals. Patients' request for antibiotic therapy is an important factor for conservative treatment. The main argument against this therapy is "medical doubts." 26% of the surgeons would treat their own appendicitis conservatively. There are distinct associations between the application of conservative therapy, satisfaction with it, and expectations about future development. The response rate was 19.9%. ***Conclusion:*** The nonoperative antibiotic therapy of appendicitis is part of clinical practice in Germany. There are differences in preconditions as well as in the acceptance of this therapeutic option with a high proportion of general rejection.

Introduction

In 1956, the surgeon Eric Coldrey presented a concept for the antibiotic therapy of acute appendicitis [1, 2]. This was reactivated following series of randomized clinical trials after 2006. In these studies, the safety of the nonoperative treatment was demonstrated, while other results were inconsistent [3–8]. At times, antibiotic therapy for appendicitis was advocated so enthusiastically that a general change of the surgical practice was discussed [9].

These studies triggered a discussion in the scientific community [10, 11]. Although a definite assessment is currently difficult, nonoperative therapy of acute appendicitis is actually being discussed more diversely. Nevertheless, current guidelines still refer to surgery as the gold standard [12].

It remains unclear to what extent antibiotic therapy of acute appendicitis is used in clinical practice. An US American analysis showed an increase in antibiotics-treated ap-

karger@karger.com
www.karger.com/vis

Dr. Alexander Reinisch
Department of General, Visceral and Oncologic Surgery
Hospital and Clinics Wetzlar
Forsthausstrasse 1, DE–35578 Wetzlar (Germany)
alexander_reinisch@hotmail.com

Table 1. Demography

		Methodically nonoperative antibiotic treatment		Nonoperative antibiotic treatment in exceptional cases		Rejection of nonoperative antibiotic treatment		*p*
		n	%	*n*	%	*n*	%	
Total		39	14	106	38.1	133	48.8	
Gender	female	4	10.3	30	28.3	37	27.8	ns
	male	35	89.7	76	71.7	96	72.2	0.017[a]
Hospital level	I, II	24	61.5	74	69.8	107	80.5	0.02[c]
	III	15	38.5	32	30.2	26	19.6	ns
Consultant for	<5 years	4	10.3	25	23.6	29	21.8	ns
	6–10 years	9	23.08	28	26.4	33	24.8	ns
	>10 years	26	66.67	51	48.1	62	46.6	ns
Federal state	MET	5	12.8	14	13.2	4	3	0.025[b] 0.002[c]
Population density	dense	12	30.8	32	30.2	55	41.4	ns
	sparse	22	56.4	60	56.6	74	55.6	ns

MET, the 5 largest metropolitan regions; ns, no significant differences. [a] Methodically nonoperative antibiotic treatment. [b] Nonoperative antibiotic treatment in exceptional cases. [c] Rejection of nonoperative antibiotic treatment.

pendicitis by 2011, while data from an US survey address this therapy only as a subordinate target [13, 14]. Beyond this, any data is lacking. Moreover, we have no information on the criteria that influence the choice of this therapy.

The aims of this study were to gain an overview of the use of antibiotic therapy for appendicitis in adults in everyday German hospital life.

Methods

The study was approved by the Institutional Review Board (AZ 204/18) and registered in the German Clinical Trials Register (DRKS00015887). One recruitment e-mail was sent to board-certified consultants for general and/or visceral surgery in German hospitals.

Out of 1,156 surgical clinics, those clinics which published the e-mail addresses of the medical staff openly were selected. These addresses were added to lists and differentiated per federal state. From each list, 80 surgeons from first- and second-level hospitals (level I and II [community/general/regional hospitals]) and 20 surgeons from third-level hospitals (level III [central/University hospitals]) were randomly selected using the Microsoft Excel® function RANDBETWEEN(X;Y) [15]. The list of surgeons from "Bremen" was incorporated into "Lower Saxonia." Another 80 + 20 surgeons were accordingly selected from hospitals in Germany's 5 largest metropolitan areas (MET): Berlin, Munich, Hamburg, Cologne, and Frankfurt. Surgeons from federal states with a high population density (>220 persons/km^2) were compared to those from states with a low population density.

The e-mail included general study information and a link to the survey (online Supplement 1; for all online suppl. material, see www.karger.com/doi/10.1159/000506058). It was clarified that only uncomplicated (not gangrenous/not perforated) appendicitis was the subject of this study. The survey was conducted in German. Incorrect or failed deliveries were replaced by newly selected addressees.

In addition to the answers, we recorded federal state/MET, hospital level (level I and II vs. III), time since board certification, and gender. The questionnaire included different question sequences (online Supplement 2). Questionnaire respondent traceability was technically impossible. The questionnaire was active for 30 working days.

A χ^2 test was used to compare nominally scaled parameters, and a Mann-Whitney U test (2 groups) or Kruskal-Wallis H test (>2 groups) was used to compare ordinally scaled parameters. A p value of <0.05 was considered statistically significant.

Results

Response

Out of 1,400 questionnaires, 278 (19.9%) were completed. The response rate was significantly higher for surgeons of level III than for surgeons of level I and II hospitals (26.1 vs. 18.7%, $p = 0.024$).

Antibiotic Therapy of Acute Appendicitis

When asked whether they treat uncomplicated appendicitis with antibiotics, 39 (14%) surgeons stated "yes" and 133 (48.8%) stated "no"; another 106 (38.1%) stated that they use antibiotic treatment "in exceptional cases." Partially significant differences between these groups of surgeons were noted (Table 1; see section Comparative Presentation).

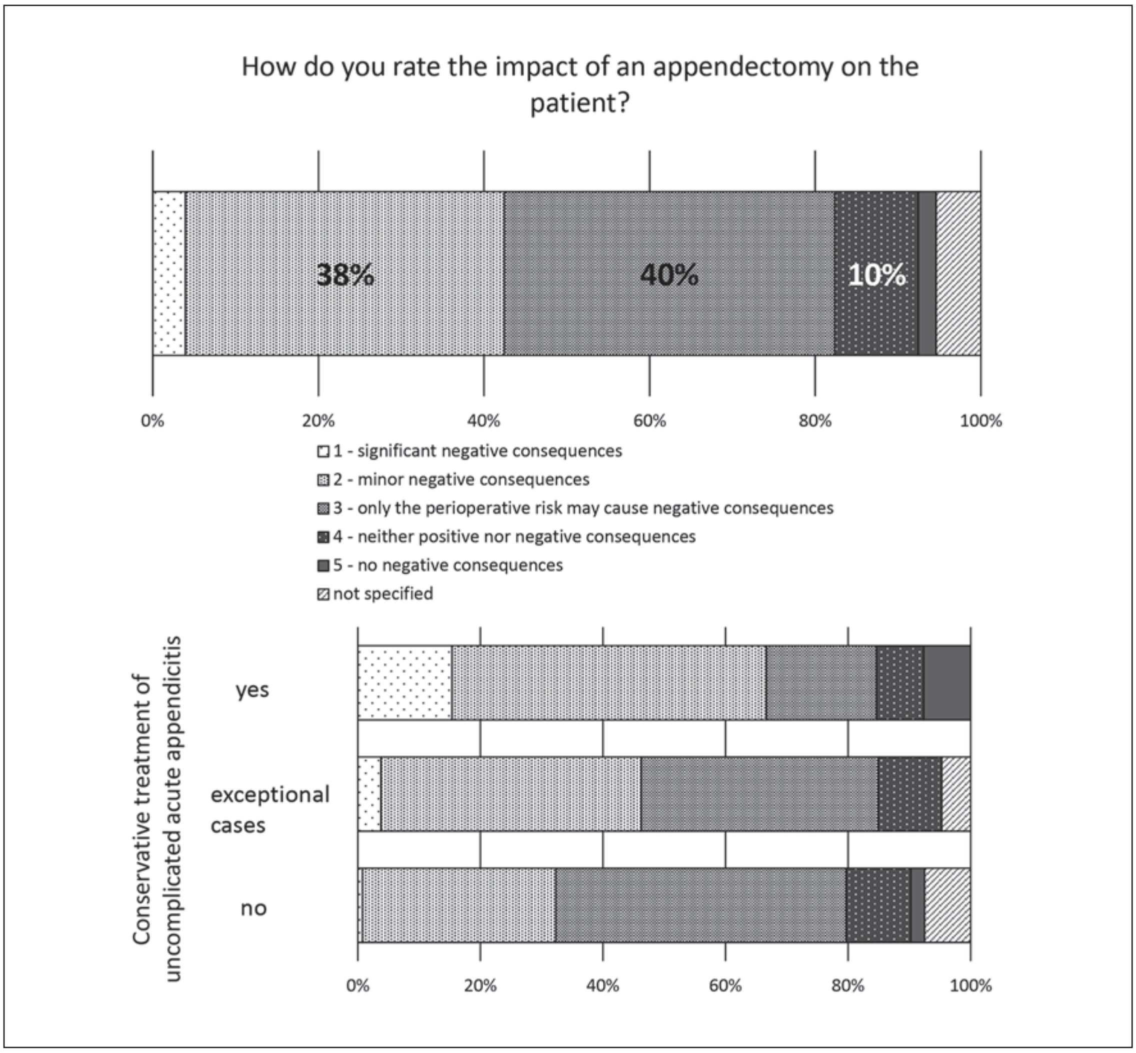

Fig. 1. Impact of appendectomy on the patient.

Methodical Antibiotic Nonoperative Therapy

Of the surgeons who methodically treat uncomplicated acute appendicitis nonoperatively, 61.5% (*n* = 24) treated 1–10%, 23.1% (*n* = 9) treated 11–20%, 10.3% (*n* = 4) treated 21–30%, and 5.1% (*n* = 2) treated up to 40% of the patients nonoperatively. On average, surgeons in this group treated 3 patients per annum. 43.6% of the surgeons only reported the proportion of patients.

At least one imaging procedure, sonography or computed tomography (CT)/magnetic resonance imaging (MRI), was mandatory for all surgeons; 84.6% requested sonography, 56.4% requested CT/MRI, and 41% both. 92.3% demanded (among other parameters) leukocyte counts and C-reactive protein. The combination of at least one imaging result with leucocyte count and C-reactive protein as well as the overall clinical impression was mandatory for 89.7% of surgeons. Temperature (38.5%) and interleukin 6/procalcitonin (5.3%) were requested less frequently.

The question regarding the most decisive factor for the consideration of a conservative therapy was answered by all surgeons. In 46.2%, the combination of surgeon's recommendation and patient's demand led to nonoperative therapy. In 30.8% the surgeon's recommendation and in 23.1% the patient's request was decisive.

79.5% of the surgeons were *rather satisfied* or *satisfied* with the results of antibiotic nonoperative treatment, and none was *rather unsatisfied* or *unsatisfied*; 20.5% did not make an assessment.

Antibiotic Nonoperative Therapy in Exceptional Cases

A total of 106 surgeons stated that they treat acute appendicitis nonoperatively in exceptional cases. The main reason for an exceptional antibiotic therapy was the *explicit and active request of the patient* (40.9%). S*pecial clinical circumstances* (19.1%), usually very mild clinical symptoms and/or a low inflammatory activity, was the second most

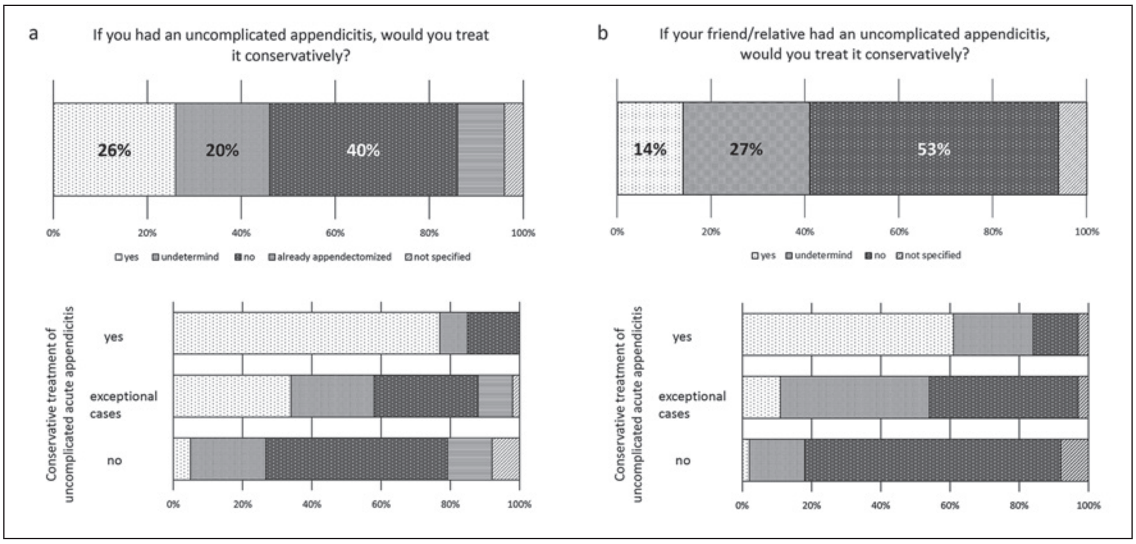

Fig. 2. a, **b** Hypothetical treatment of appendicitis.

frequently stated reason, and 18.2% stated an *exceptionally high perioperative risk* as the reason for a conservative therapy. In 19.1%, the combination of the patient's request and high perioperative risk led to such a therapy.

97.2% explained why they do not methodically treat appendicitis conservatively. 51% reported *medical doubts* about this therapy. *Legal concerns* were ranked second with *ambiguous scientific evidence* (each 39%), and 14% stated that they had *too few suitable patients*. A total of 11.3% were concerned about *accounting*.

60.9% of MET hospital surgeons offered nonoperative treatment in exceptional cases; this proportion is significantly higher than that of other regions (total 36.8%, p = 0.024).

Rejection of Antibiotic Nonoperative Therapy

A total of 133 surgeons stated that they never treat uncomplicated acute appendicitis conservatively. The main reason for rejection was *medical doubt* (68%). *Ambiguous scientific evidence* and concerns about *legal consequences* were named by 39%; 18% stated that this treatment option is *generally rejected by their clinic*. Uncertainties regarding *accounting* were stated by 10%.

Significantly more level I and II surgeons than level III surgeons rejected this therapy (80.6 vs. 19.6%, p = 0.02).

Comparative Presentation

Differences between the surgeons who regularly/methodically, in exceptional cases, or not at all treated appendicitis nonoperatively were analyzed (Table 1).

Demography

The proportion of male surgeons who methodically treated appendicitis nonoperatively was significantly higher than that of female surgeons (Table 1; 16.9 vs. 5.6%, p = 0.017). Distribution according to the period of board certification did not differ significantly.

In relation to all groups (methodical conservative treatment, conservative treatment in exceptional cases, rejection of conservative therapy), more level III hospital surgeons methodically treated appendicitis nonoperatively compared to level I and II surgeons, but this difference did not reach significance (20.6 vs. 11.7%, p = 0.076). Significantly more level I and II hospital surgeons rejected antibiotic treatment (52.2 vs. 35.6%, p = 0.02). Significantly more surgeons from MET treated appendicitis methodically or in exceptional cases conservatively compared to those not from MET (82.6 vs. 52.2%, p = 0.002).

Assumed Consequences of Appendectomy

Surgeons who treat appendicitis methodically nonoperatively consider the consequences of appendectomy to be significantly more severe than those who treat conservatively only in exceptional cases or never (Fig. 1; 5 – no negative consequences vs. 1 – significant negative consequences, methodically: 2.41 ± 1.09 vs. exceptional cases: 2.58 ± 0.574 vs. never: 2.8 ± 0.743, $p < 0.001$). Surgeons working in MET assess the effects of an appendectomy to be significantly graver for the patient (MET vs. rest, 2.48 ± 0.898 vs. 2.68 ± 0.803, p = 0.001).

Therapy of Appendicitis in Oneself and Related Persons

Surgeons were questioned on nonoperative treatment for hypothetical appendicitis in themselves or a friend/relative as an indirect parameter for the attitude towards this therapy. 26% selected antibiotic therapy for themselves, 40% rejected the nonoperative therapy, 20% were

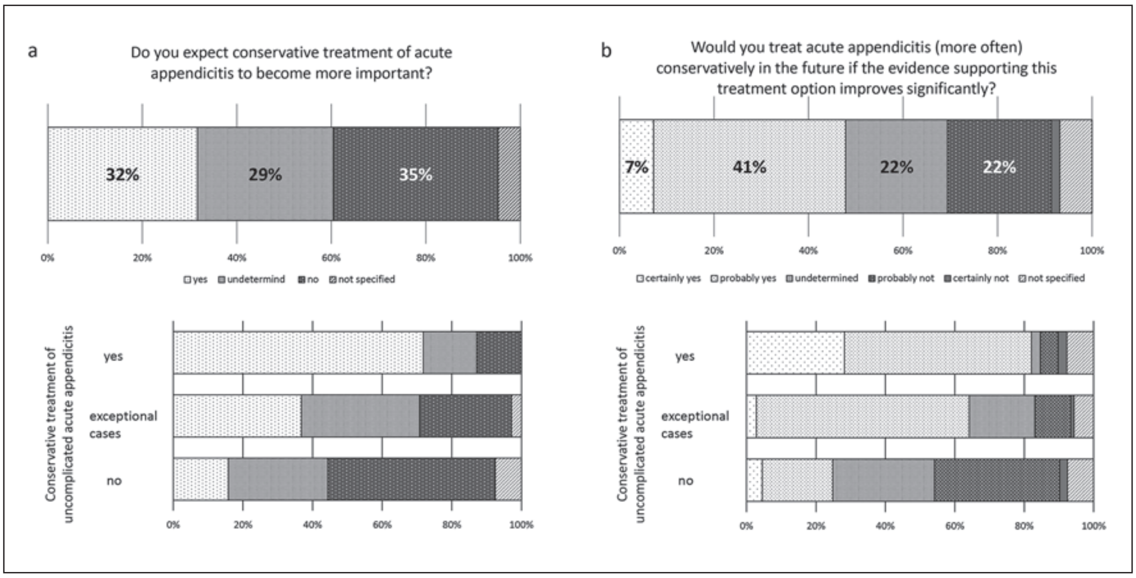

Fig. 3. a Expectations of future importance. **b** Expectations of future application.

undecided, and 10% were appendectomized. Proportions of surgeons who would treat the hypothetical appendicitis of a friend/relative nonoperatively differ slightly (Fig. 2a, b).

Conservative treatment of themselves and relatives is chosen significantly more often by surgeons who apply this form of therapy (*methodically* vs. *exceptional cases* vs. *never*, $p < 0.0001$; *exceptional cases* vs. *never*, $p < 0.0001$). If a surgeon did not perform a conservative therapy, she/he rejected this treatment significantly more often for herself/himself or relatives ($p = 0.0002$ and $p = 0.025$).

Surgeons with 6–10 years of experience ($p = 0.14$), from level III hospitals ($p = 0.013$), and female surgeons ($p = 0.026$) would use antibiotic treatment on themselves at a significantly higher rate. General rejection was found more often in level I and II hospital surgeons (64.1 vs. 43.5%, $p = 0.004$).

Surgeons who would treat appendicitis in themselves conservatively considered the consequences of appendectomy to be significantly more serious than those who would not treat themselves nonoperatively (2.31 ± 0.383 vs. 2.81 ± 0.803, $p < 0.0001$).

Expectations about Future Trends

35% of surgeons do not expect antibiotic treatment to become more important in the future. 32% expect an increase in importance, i.e., more often, surgeons actually using this therapy (71.8%, $p < 0.0002$) and those from MET ($p = 0.001$) (Fig. 3a).

Surgeons who routinely use antibiotic appendicitis therapy state that they will use this therapy more often if the evidence improves (Fig. 3b) compared to those who currently reject this therapy or use it in exceptional cases (4.11 ± 0.894 vs. 3.57 ± 0.785 vs. 2.88 ± 0.946, $p < 0.0001$). Surgeons from MET (3.74 ± 0.689 vs. 3.29 ± 1.001, $p = 0.027$) as well as those from level III hospitals (3.58 ± 0.881 vs. 3.23 ± 1.006, $p = 0.008$) state that they would perform this therapy more frequently given improved evidence.

Discussion/Conclusion

After more than 100 years of successful surgical therapy of acute appendicitis, nonoperative antibiotic therapy is increasingly discussed and also applied [11]. However, little is known about nonoperative therapy for uncomplicated appendicitis in everyday clinical practice [14]. Our study provides valuable information on this topic by using an approved examining technique: a survey among clinically active surgeons. The response rate of 19.9% was comparable to other surveys in surgery [16].

In our study, antibiotic nonoperative treatment of uncomplicated appendicitis is remarkably well accepted among the surveyed surgeons. By summing up those surgeons who methodically or exceptionally treat appendicitis conservatively, more than 50% of the surgeons use this therapeutic option. This differs clearly from the reported rate of 15% in the USA by Yeh et al. [14].

The rate of surgeons that are *rather satisfied* or *satisfied* with the antibiotic therapy is high (79.5%); none are dissatisfied. This is notable, especially against the background of reported recurrence rates of 39% within 5 years, which cannot be regarded as very satisfactory [17].

For all that, it remains interesting that even the surgeons who regularly use antibiotic treatment treat only one small subgroup of their patients nonoperatively; 84.6% treated under 20% of their patients conservatively. This is consistent with the largest study by Salminen et al. [5] in which only 5.8% of the 4,380 appendicitis patients were treated with antibiotics.

Our data provide a clear indication that this form of therapy is quite applicable in Germany and that its users are satisfied. It remains unclear what triggers this satisfaction.

For the first time, data on decision-making on nonoperative therapy are available. Surgeons who methodically treat nonoperatively often decide on this therapy together with their patients. In approximately half of the cases, the decision on nonoperative therapy is made jointly by the patient and the surgeon. In less than one-third of the cases, the surgeon's recommendation is crucial.

Surgeons who treated appendicitis in *exceptional cases* nonoperatively were asked for their "exception criteria." The main motivation named was the *explicit and active patient request* (40%), followed by rather *low level of inflammatory activity* (19.1%) or *patient-related high risk* (18.2%). This indicates that the patient is widely involved in the choice of treatment.

After all, the largest group of surgeons in this survey never uses nonoperative antibiotic treatment of appendicitis (48.8%). In this group, as among those who treat nonoperatively only in exceptional cases, we asked for the reasons for the critical attitude. The main reason were *medical doubts* (general refusal 68%, exceptional cases 51%). This is reasonable in the light of the current studies and meta-analyses that show relevant therapy failure and recurrence rates [18–20]. *Insufficient scientific evidence* (general refusal 40%, exceptional cases 39%) is named in second place together with *medico-legal concerns* [19]. A clear legal assessment of this therapy is currently impossible. In Germany, by now the medico-legal risks of omitted surgery for appendicitis are emphasized [21, 22].

Of particular interest are our findings which reflect the surgeons' attitude towards antibiotic therapy of uncomplicated acute appendicitis. Surgeons who regularly treat appendicitis conservatively consider the consequences of an appendectomy as graver than those who do not. Some studies show an increased complication rate in appendectomized compared to antibiotics-treated patients; however, long-term adverse consequences of appendectomy are unclear [23, 24].

We asked the surgeons how they would treat themselves or their relatives. The results correlate with the application of antibiotic therapy for appendicitis. The proportion of surgeons who answered "yes" for self-treatment was even higher than the proportion of those who practice this form of therapy.

Looking at the subgroups of surgeons who regularly/exceptionally/never use nonoperative therapy shifts the ratios distinctly. Only 5% of surgeons who reject antibiotic therapy in professional life would treat their own appendicitis conservatively, while 61% of those who perform this therapy would use it for themselves. These results are in contrast to findings in a general population survey in which 9.4% of respondents wanted antibiotic treatment for themselves [25].

Finally, we asked about expectations about the future. One-third expect this therapy to become more important, one-third does not. Again, there are significant differences between surgeons using antibiotic therapy and those who do not or only in exceptional cases. Interestingly, approximately half of the surgeons say that they would use this therapy more often, if the evidence for antibiotic therapy improved. It is unclear what prompted this positive attitude, since actual data provides only limited cause for positive expectations [17, 26]. Among the surgeons who never use nonoperative antibiotic therapy, the attitude on this therapy is comparatively critical, even with improved evidence. Our study indicated that surgeons working in level III or MET hospitals are more positive about nonoperative therapy of uncomplicated appendicitis. The data collected and the current literature do not provide a conclusive explanation for this observation. Further studies, such as focused interviews with surgeons, may help to understand what causes the different attitudes to this therapy.

There are some limitations to this study. The response rate was relatively low. However, this is an effect of the broad and only specifically preselected survey. Comparable studies which surveyed only members of a professional society achieved higher response rates, but this is associated with a relevant selection bias [14].

Although questions were formulated to minimize response bias, the effects of question order bias and especially social desirability bias cannot be completely ruled out [27]. The survey reflects the situation in Germany. The health system in Germany gives the surgeon extensive freedom in decisions about therapeutic procedures, so, these German results are of explicit interest. However, it would be important to study this topic in other countries as well.

This is the first overview of the use of antibiotic therapy for acute appendicitis in clinical practice. It was possible to gather information about factors that influence surgeons' decisions and describe their general attitude. Antibiotic nonsurgical treatment of acute appendicitis is part of clinical practice; however, we could not notice a general change in surgical practice as assumed by some authors [9]. However, the study shows that the surveyed surgeons are deeply divided in terms of the application but also the assessment of this form of therapy.

Statement of Ethics

The published research complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The study was approved by the Review Board of the Justus Liebig University Giessen (AZ 204/18) and registered in the German Clinical Trials Register (DRKS00015887).

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding or sponsoring was obtained.

Author Contributions

Study conception and design: A. Reinisch, J. Liese. Drafting of the manuscript: A. Reinisch, J. Liese. Acquisition of data: A. Reinisch, M. Reichert. Analysis and interpretation of data: A. Reinisch, M. Reichert, A. Hecker, J. Liese. Critical revision of the manuscript: J. Liese, F. Ulrich, W. Padberg. Final approval of the version to be submitted: all authors.

References

1 Coldrey E. Treatment of acute appendicitis. BMJ. 1956 Dec;2(5007):1458–61.
2 Coldrey E. Five years of conservative treatment of acute appendicitis. J Int Coll Surg. 1959;32:255–61.
3 Di Saverio S, Sibilio A, Giorgini E, Biscardi A, Villani S, Coccolini F, et al. The NOTA Study (Non Operative Treatment for Acute Appendicitis): prospective study on the efficacy and safety of antibiotics (amoxicillin and clavulanic acid) for treating patients with right lower quadrant abdominal pain and long-term follow-up of conservatively treated suspected appendicitis. Ann Surg. 2014 Jul;260(1):109–17.
4 Vons C, Barry C, Maitre S, Pautrat K, Leconte M, Costaglioli B, et al. Amoxicillin plus clavulanic acid versus appendicectomy for treatment of acute uncomplicated appendicitis: an open-label, non-inferiority, randomised controlled trial. Lancet. 2011 May;377(9777):1573–9.
5 Salminen P, Paajanen H, Rautio T, Nordström P, Aarnio M, Rantanen T, et al. Antibiotic Therapy vs Appendectomy for Treatment of Uncomplicated Acute Appendicitis: The APPAC Randomized Clinical Trial. JAMA. 2015 Jun;313(23):2340–8.
6 Styrud J, Eriksson S, Nilsson I, Ahlberg G, Haapaniemi S, Neovius G, et al. Appendectomy versus antibiotic treatment in acute appendicitis. a prospective multicenter randomized controlled trial. World J Surg. 2006 Jun;30(6):1033–7.
7 Hansson J, Körner U, Khorram-Manesh A, Solberg A, Lundholm K. Randomized clinical trial of antibiotic therapy versus appendicectomy as primary treatment of acute appendicitis in unselected patients. Br J Surg. 2009 May;96(5):473–81.
8 Turhan AN, Kapan S, Kütükçü E, Yiğitbaş H, Hatipoğlu S, Aygün E. Comparison of operative and non operative management of acute appendicitis. Ulus Travma Acil Cerrahi Derg. 2009 Sep;15(5):459–62.
9 Hansson J, Körner U, Ludwigs K, Johnsson E, Jönsson C, Lundholm K. Antibiotics as first-line therapy for acute appendicitis: evidence for a change in clinical practice. World J Surg. 2012 Sep;36(9):2028–36.
10 Flum DR. Clinical practice. Acute appendicitis—appendectomy or the "antibiotics first" strategy. N Engl J Med. 2015 May;372(20):1937–43.
11 McBurney C. Experiences with early operative interference in cases of disease of the vermiform appendix. N Y Med J. 1889;50:676–84.
12 Gorter RR, Eker HH, Gorter-Stam MA, Abis GS, Acharya A, Ankersmit M, et al. Diagnosis and management of acute appendicitis. EAES consensus development conference 2015. Surg Endosc. 2016 Nov;30(11):4668–90.
13 Khalil M, Rhee P, Jokar TO, Kulvatunyou N, O'Keeffe T, Tang A, et al. Antibiotics for appendicitis! Not so fast. J Trauma Acute Care Surg. 2016 Jun;80(6):923–32.
14 Yeh DD, Sakran JV, Rattan R, Mehta A, Ruiz G, Lieberman H, et al. A survey of the practice and attitudes of surgeons regarding the treatment of appendicitis. Am J Surg. 2019 Jul;218(1):106–112.
15 McCord C, Ozgediz D, Beard J. General surgical emergencies. In: Debas HT, Donkor P, Gawande A, editors. Essential Surgery: Disease Control Priorities. 3rd ed. Vol 1. Washington (DC): The International Bank for Reconstruction and Development/The World Bank; 2015.
16 Faivre G, Marillier G, Nallet J, Nezelof S, Clment I, Obert L. Are French orthopedic and trauma surgeons affected by burnout? Results of a nationwide survey. Orthop Traumatol Surg Res. 2019 Apr;105(2):395–9.
17 Salminen P, Tuominen R, Paajanen H, Rautio T, Nordström P, Aarnio M, et al. Five-Year Follow-up of Antibiotic Therapy for Uncomplicated Acute Appendicitis in the APPAC Randomized Clinical Trial. JAMA. 2018 Sep;320(12):1259–65.
18 Podda M, Gerardi C, Cillara N, Fearnhead N, Gomes CA, Birindelli A, et al. Antibiotic Treatment and Appendectomy for Uncomplicated Acute Appendicitis in Adults and Children: A Systematic Review and Meta-analysis. Ann Surg. 2019 Dec;270(6):1028–40.
19 Poprom N, Numthavaj P, Wilasrusmee C, Rattanasiri S, Attia J, McEvoy M, et al. The efficacy of antibiotic treatment versus surgical treatment of uncomplicated acute appendicitis: systematic review and network meta-analysis of randomized controlled trial. Am J Surg. 2019 Jul;218(1):192–200.
20 Poon SH, Lee JW, Ng KM, Chiu GW, Wong BY, Foo CC, et al. The current management of acute uncomplicated appendicitis: should there be a change in paradigm? A systematic review of the literatures and analysis of treatment performance. World J Emerg Surg. 2017 Oct;12(1):46.
21 Vinz H, von Bülow M, Neu J. [Delayed appendectomy because of diagnostic malpractice: Experiences of the Arbitration Board of the North German Medical Associations]. Z Evid Fortbild Qual Gesundhwes. 2015;109(9-10):704–13.
22 Glatz U. [Uncomplicated appendicitis: is surgery always necessary?]. Dtsch Med Wochenschr. 2014 Aug;139(34-35):1697.
23 Antibiotic therapy for acute appendicitis in adults. Fewer immediate complications than with surgery, but more subsequent failures. Prescrire Int. 2014 Jun;23(150):158–60.
24 Rasmussen T, Fonnes S, Rosenberg J. Long-Term Complications of Appendectomy: A Systematic Review. Scand J Surg. 2018 Sep;107(3):189–96.
25 Hanson AL, Crosby RD, Basson MD. Patient Preferences for Surgery or Antibiotics for the Treatment of Acute Appendicitis. JAMA Surg. 2018 May;153(5):471–8.
26 Ceresoli M, Pisano M, Allievi N, Poiasina E, Coccolini F, Montori G, et al. Never put equipoise in appendix! Final results of ASAA (antibiotics vs. surgery for uncomplicated acute appendicitis in adults) randomized controlled trial. Updates Surg. 2019 Jul;71(2):381–387.
27 Furnham A. Response bias, social desirability and dissimulation. Pers Individ Dif. 1986;7(3):385–400.

European Journal of Trauma and Emergency Surgery (2022) 48:3033–3042
https://doi.org/10.1007/s00068-022-01878-2

ORIGINAL ARTICLE

Frailty in elderly patients with acute appendicitis

Alexander Reinisch[1] · Martin Reichert[2] · Christian Charles Ondo Meva[3] · Winfried Padberg[2] · Frank Ulrich[1,3] · Juliane Liese[2]

Received: 13 June 2021 / Accepted: 4 January 2022 / Published online: 2 February 2022

Abstract

Purpose Acute appendicitis in the elderly is becoming increasingly recognized for its often severe course. For various elective and urgent operations in older patients, frailty is a risk factor for poor outcomes. However, there is a lack of data on frailty in elderly patients with acute appendicitis.

Methods Patients over 65 years old who underwent surgery for acute appendicitis in three hospitals between January 2015 and September 2020 were assessed with the Hospital Frailty Risk Score (HFRS) and the modified Frailty Index (mFI). Outcomes of interest, including morbidity, mortality, and length of stay, were recorded.

Results While frailty can be measured with both tests, the mFI has better applicability and takes significantly less time to implement compared to the HFRS (21.6 s vs. 80.3 s, $p<0.0001$) while providing the same information value.

Patients who exhibited frailty according to either assessment had a significantly higher rate of milder (OR 5.85/2.87, $p<0.0001/0.009$) and serious (OR 4.92/3.61, $p<0.011/0.029$) complications, more admissions to the intensive care unit (OR 5.16/7.36, $p<0.0001$), and an almost doubled length of stay (12.7 days vs. 6.6 days, $p<0.005$). Up to 31% of these patients required institutional care after discharge, which is significantly more than those without frailty ($p<0.0001$). Furthermore, the mortality rate in frail patients was significantly elevated to 17%, compared to less than 1% in non-frail patients ($p=0.018$).

Conclusion In elderly patients, frailty is a significant risk factor for negative outcomes. Frailty can be assessed more quickly and reliably with the mFI compared to the HFRS.

Keywords Appendicitis · Frailty · Surgery · Geriatric

Introduction

The unique challenges of treating elderly patients with acute appendicitis are not obvious. However, it is becoming increasingly understood that acute appendicitis, despite its maximum incidence in young adulthood, is a significant illness with very unfavorable outcomes in the elderly population [1, 2]. As the number of elderly individuals, mostly defined as people over 65 years of age, is continuously increasing in developed countries, acute appendicitis in the elderly and its associated challenges will become more prevalent [3, 4]. Thus, the long-prevailing notion that appendicitis is a disease of the young is partly outdated [5].

Acute appendicitis in the elderly differs from that in young people; more complicated appendicitis with perforations is observed in older patients [6]. The more decisive factor, however, is the association between old age and poor outcomes. Among other challenges, older patients suffer from a complication rate of up to 25%, require longer hospital treatment than younger patients, and have a marked mortality rate of up to 8–16% [4, 7, 8].

This illustrates the particular importance of understanding appendicitis in older people, a fact that is also reflected in issuing a special guideline for appendicitis in older people [9].

Special and unfavorable courses in the treatment of older people are explained less by the *numerical age* than by the

✉ Alexander Reinisch
alexander_reinisch@hotmail.com

1 Department of General, Visceral and Oncologic Surgery, Hospital and Clinics Wetzlar; Teaching Hospital of the JLU Giessen, Wetzlar, Germany

2 Department of General, Visceral, Thoracic, Transplant and Pediatric Surgery, University Hospital Giessen, Giessen, Germany

3 Department of General, Visceral and Oncologic Surgery, Dill-Clinics, Dillenburg, Germany

biological age. For some elderly patients, the risk of an unfavorable outcome of treatment goes far beyond the risk inherent in the disease and higher age itself [10]. An approximation to *biological age* can be achieved in part by measuring *frailty*. Frailty has established itself as a multidimensional syndrome and can be summarized as an age-related "consequence of dysregulation in several physiological control circles", leading to lower resilience and increased vulnerability to stressors [11, 12]. The *physical phenotype model of frailty* (Fried) includes physical aspects and mental and social factors but the scope and weighting of these factors are not clearly defined.

Emergency surgery is a significant stressor even for young and healthy patients. Frail patients are even more vulnerable and less resilient to emergency surgery as it has been shown that frailty is an independent risk factor for negative outcomes. This applies not only for medical factors (e.g., complications) but also for social aspects, such as the opportunity to return to one's usual living environment [13]. Few studies have investigated the role of frailty in emergency general surgery patients. In a recent study, Fagenson et al. showed that frailty is a factor for negative outcomes in acute cholecystitis. Murphy et al. and Sánchez Arteaga et al. evaluated different emergency general surgery operations and found similar results [14, 15]. Other studies have shown that frailty is a risk factor for, inter alia, morbidity and mortality [16–19]. However, either unreported or playing only a subordinate role in these studies, appendicitis has yet to be fully addressed.

Frailty can be framed as "reduced performance" (Fried) and as an "accumulation of deficits" (Rockwood) [12, 20]. There are over 70 validated assessments available to determine frailty, however, none of which have been established as the gold standard. Approximately half of these have been used on surgical patients [21]. Many established tests are not suitable for patients in an acute situation because they often refer to a period of several weeks before testing and are biased by acute illness. Several other tests (e.g., Edmonton Frail Scale, CSHA-Frailty index, LUCAS) require the active participation of the patient and are often complex and time-consuming [20, 22, 23]. Easily scaled assessments (e.g., the CSHA scale) are relatively subjective and more suitable for situations in which the patient can be assessed by a family doctor over a long period.

To investigate possible relationships between frailty and acute appendicitis, we had to choose assessments that were retrospectively feasible with routinely recorded data. After the pool of possible assessments was narrowed due to the above restrictions, we chose two tools for this study: (1) the *Hospital Frailty Risk Score (HFRS)* and (2) the *modified Frailty Index (mFI)*, where the latter is relatively simpler than the former.

The mFI [20, 24] records 11 parameters (mFI-11) in the classic version, but a simplified form with only 5 parameters is available (mFI-5) [25]. The advantage of the mFI is that it is not biased by the patient's acute illness and can be recorded by non-geriatric specialists based on information available in the emergency room. This also applies to the HFRS. While the HFRS has the same requirements as the mFI, it is much more complex with over 100 parameters of different weight [26].

The aim of this study was to analyze frailty as a possible risk factor in the treatment of elderly patients with acute appendicitis. Identifying high-risk patients during admission with a reliable assessment can, if necessary, optimize the peri- and postoperative care of these patients.

Methods

We conducted a retrospective analysis of all patients who underwent surgery for acute appendicitis at one of three participating centers between January 1, 2015, and September 30, 2020. All data were extracted from electronic patient records. Frailty assessment was conducted based on emergency room recording sheets, premedication sheets, and findings made at admission. Only information that was available to the admitting doctor in the emergency room was used in the frailty assessment.

Inclusion criteria

- Admission and operation for acute appendicitis.
- Age of 65 years or older on the day of admission.
- Complete hospital record including laboratory results, pathological results, insurance data, and data on abidance after dismission.
- Possibility of a complete follow-up of 90 days after the operation.
- Readmitted patients: cause of readmission (surgical vs. alternative).

Exclusion criteria

- Further planned surgery or intervention during follow-up.
- Scheduled inpatient readmission during follow-up.

All patients were assessed independently by two authors (AR and JL). Patients with a discrepant score/index were reassessed by another randomly selected author, and the majority vote (two out of three) was used. All patients could be evaluated using this technique.

The time necessary to conduct the HFRS and the mFI was recorded. To minimize errors due to learning effects when performing the assessments, the authors were randomly assigned the patient and the respective test (HFRS or mFI) using a computer algorithm.

The HFRS is based on the *International Classification of Diseases* (ICD) codes. The queried electronic patient files do not often explicitly state the corresponding ICD code; however, the ICD code can be determined using the ICD-10 manual, 10th Revision, German Modification (ICD-10-GM). This back-coding was not taken into account when determining the assessment time.

The text in the electronic patient records and the ICD codes often do not exactly match the codes given in the HFRS, even if the conditions are clearly the same [e.g., M15(0.9)—HFRS 0.4 points vs. M19(0.9)—HFRS 1.5 points]. In addition, very broad diagnoses can be found in the HFRS (e.g., Z91: Personal history of risk factors, not elsewhere classified, R69 Unknown and unspecified causes of morbidity, Z87: Personal history of other diseases and conditions). Comparable inaccuracies can theoretically arise when transferring the electronic patient records to the mFI.

To document these inaccuracies, the accuracy of the diagnosis–assessment–transfer was estimated and classified by the authors according to the following categories: *high* for > 75% exact code agreement, low interpretation of the diagnosis codes; *intermediate* for > 50%—< 75% exact code agreement, significant need for interpretation; and *low* for predominantly interpreted diagnosis codes. Discrepant assessments were reconciled based on a majority decision with the addition of a third reviewer in the abovementioned manner.

The outcomes of interest were mortality; complications according to the Dindo/Clavien classification (CD) of surgical complications [27]; admittance to an intensive care unit (ICU); length of stay in the ICU; overall length of hospital stay (LOS); whether the patient was discharged home, to the same type of facility from which she or he originated or a facility of a higher care level; readmittance within 30 or 90 days after the operation; and readmittance due to a surgical/operation-related or an alternative reason.

The abovementioned outcome variables were analyzed against the following covariates: sex; complicated (perforated/gangrenous) vs. uncomplicated appendicitis (histopathology); open vs. laparoscopic vs. conversion laparoscopic-open surgery; unsuspected histopathological or intraoperative findings; health insurance (private vs. statutory); white blood cell count; and C-reactive protein (CRP) at admission.

Comorbidities were analyzed using the *Charlson Comorbidity Index* (CCI). Since this study focused on patients over the age of 65, the age-adjusted CCI was waived as applying it would introduce bias [28].

Statistical analysis

The patient demographics were expressed as the mean ± standard deviation (SD) or as the median and range, as appropriate. Fisher's exact test was used to analyze the differences in categorical variables. The Student's *t* test was applied to variables that were normally distributed. The Mann–Whitney *U* test was applied to non-normally distributed variables. Binary logistic respective linear regression analysis was conducted to determine odds ratios (OR), and qualitative classification was carried out by *receiver operating characteristic* (ROC) analysis. Unless otherwise indicated, all tests were two tailed, and p values < 0.05 were considered significant. All data were analyzed with SPSS, version 27 (IBM, Armonk, NY, USA).

Results

Demographic parameters

A total of 2,089 patients were included in the retrospective analysis at three centers. The mean age was 32.7 years (SD 20.2 years, range 2.1–98.6 years). Of these, 213 (10.2%) were 65 years or older at the time of the operation, 32 patients were excluded (see methods section). Between the three centers, there were no significant differences in patient characteristics, operative aspects, or any of the outcome parameters.

The characteristics of the 181 included patients are shown in Table 1.

Frailty assessment

All included patients were evaluated with the abovementioned frailty assessments. The same scores were assessed by the authors for HFRS in 95.6% of the cases and for mFI-11 or mFI-5 in 97.2% of the cases. A majority decision was obtained for all the remaining cases. Of the 181 patients, 33 (18.2%) exhibited no indication of frailty. The mean score for the HFRS was 3.3 (SD 3.5, range 0–15.9). The mean score for the mFI-11 was 1.7 (SD 1.6, range 0–7) and that for the mFI-5 was 1.2 (SD 1.1, range 0–5). The CCI, which was used as a covariate, had a mean value of 1.7 (SD 2.1, range 0–12). The accuracy of the transferability of the diagnoses from the electronic patient record to the assessments differed significantly. The transferability to mFI-11 hat a "high" accuracy in 96.7% and "intermediate" accuracy in 3.3% of the patients. Meanwhile, the HFRS had a "high" transferability-accuracy in 17.1%, an "intermediate" accuracy in 25.4% and a "low" accuracy in 57.5% of the patients ($p < 0.0001$). The time required in seconds (sec) to carry out

Table 1 Patient characteristics

	n	%	Mean (SD; min/max)
Total patients	2089		
included patients ≥ 65 years ("elderly patients")	181	8.7	
Elderly patients			
Age			
Years			75.8 (7.5; 65.1/97.4)
Sex			
Females	90	49.7	
Males	91	50.3	
Operation			
Laparoscopic	163	90.1	
Conversion	8	4.4	
Open	10	5.5	
Complicated appendicitis[†]	113	60.4	
Unsuspected intraoperative findings[††]			
Any	28	15.5	
Malignancy	14	7.7	
Length of stay			
Days			8.2 (7.7; 0/76)
Morbidity			
Any	34	18.8	
Mortality			
90 d	5	2.8	

d days, *min* minimum, *max* maximum, *SD* standard deviation

[†]Perforated or gangrenous appendicitis

[††]In addition to an appendicitis

the assessment also differed significantly; the HRFS took an average of 80.3 s (SD 53.3 s, range 0–220 s) while the mFI-11 took an average of 21.6 s (SD 10, range 0–45 s, $p < 0.0001$).

Cutoffs were as follows:

HFRS: ≥ 5—intermediate frailty risk; ≥ 15—high frailty risk.
mFI-11: 0—no frailty; 1—prefrailty; ≥ 3 frailty.
mFI-5: 0—no frailty; 1—prefrailty; ≥ 2 frailty.

Relationship between frailty and the postoperative outcome

For the frailty assessments used, significant correlations between the most important outcome variables after appendectomy and frailty were found.

An HFRS ≥ 5 correlates with significantly more frequent overall and serious complications (CD ≥ I: % vs. 16.8%; $p < 0.0001$ resp. CD ≥ III: 18% vs. 3.8%; $p = 0.003$). Patients with an HFRS ≥ 5 were significantly more likely to be admitted to the ICU postoperatively (56% vs. 15.3%, $p < 0.0001$), and stay longer in the ICU; however, this difference was not significant [mean 7.1 days (SD 14.2 days) vs. 2.3 days (SD 1.8 days), $p = 0.086$]. Ten percent of the patients with HFRS ≥ 5 died within 90 days after the operation (vs. 0% HFRS < 5, $p < 0.0001$). With an HFRS ≥ 5, the LOS was significantly longer [12.7 days (SD 11.1 days) vs. 6.6 days (SD 4.9 days), $p = 0.001$], and these patients were more likely to be discharged to an institution with a higher care level than before admission (31.1% vs. 6.1%, $p < 0.0001$). The readmission rate was not significantly elevated. Only two patients had an HFRS ≥ 15, and both had an unfavorable outcome.

In a subgroup analysis of patients older than 75 years ($n = 89$), the abovementioned differences were confirmed but with slightly different significance values.

Patients with an mFI-11 ≥ 3 were more likely to suffer from complications (CD ≥ I 48.8% vs. 22.9%; $p = 0.003$ resp. CD ≥ III 17.1% vs. 5%, $p = 0.018$) or need admission to the ICU and with a longer stay [58.5% vs. 10.7%; $p = 0.018$, ICU-LOS 4.6 days (SD 12.2 days) vs. 0.4 days (SD 1.2 days), $p < 0.0001$]. Differences in length of ICU stay were found between patients with 1 point vs. 0 points [ICU admittance 33.1% vs. 8.5%, $p < 0.0001$; ICU-LOS 5.5 days (SD 11.5 days) vs. 1.5 days (SD 1 day), $p = 0.034$]. Significantly increased mortality was observed in patients with an mFI-11 ≥ 3 (17% vs. 0.7%, $p = 0.018$). Patients with an mFI-11 ≥ 3 stayed significantly longer in the hospital [12.7 days (SD 12.4 days) vs. 6.9 days (SD 5.1 days), $p = 0.005$] and were more often discharged to a facility with a higher care level (29.7% vs. 7.9%, $p = 0.001$; mFI ≥ 1: 16.3% vs. 2.1%, $p = 0.001$). Significant differences in readmission rates could not be observed using the mFI-11.

An mFI-5 ≥ 2 points was correlated with a greater proportion of patients with complications; the difference was significant for CD ≥ I (41.7% vs. 22.3%, $p = 0.009$) and with a trend for CD ≥ III (CD ≥ III 13.3% vs. 4.9%, $p = 0.073$ n. s.). Patients with an mFI-5 ≥ 2 were significantly more often admitted to the ICU (49.2% vs. 15.7, $p < 0.0001$); however, the length of stay in the ICU did not differ significantly. Mortality was significantly elevated in patients with an mFI-5 ≥ 2 (6.7% vs. 0.8%, $p = 0.042$). The LOS was significantly longer in the mFI-5 ≥ 2 group [11.4 days (SD 11.4 days) vs. 6.7 days (SD 4.2 days), $p < 0.0001$], and these patients were more often discharged to an institution with a higher level of care than before admission (25% vs. 6.7%, $p = 0.001$). Overall, readmissions or readmissions for nonsurgical reasons were not significantly elevated in this subgroup, but there were more readmissions for surgical reasons, most frequently for late-onset postoperative complications (26.7% vs. 14.5%, $p = 0.043$).

The observed effects were subject to univariate and multivariate regression analyses. The covariates tested were age, CCI, complicated vs. uncomplicated appendicitis, operative technique, white blood cell count and/or CRP at admission,

Table 2 Univariate and multivariate regression analysis for outcome variables related to frailty assessments

	Univariate			Multivariate		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Complications CD ≥ 1						
HFRS ≥ 5	7.43	3.59–15.39	< .0001	5.85	2.68–12.77	< .0001
mFI-11 ≥ 1	1.99	.89–4.49	n.s	–	–	–
mFI-11 ≥ 3	3.21	1.55–6.66	.002	2.87	1.3–6.32	.009
mFI-5 ≥ 2	2.49	1.27–4.85	.008	2.36	1.13–4.92	.022
Complications CD ≥ 3						
HFRS ≥ 5	5.53	1.75–17.45	.004	4.92	1.45–16.66	.011
mFI-11 ≥ 1	2.21	.48–10.28	n.s	–	–	–
mFI-11 ≥ 3	3.91	1.29–11.9	.016	3.61	1.14–11.45	.029
mFI-5 ≥ 2	2.95	.974–8.93	n.s	–	–	–
ICU admission						
HFRS ≥ 5	7	3.36–14.58	< .0001	5.16	2.31–11.54	< .0001
mFI-11 ≥ 1	5.31	1.79–15.75	.003	5.44	1.63–18.13	.006
mFI-11 ≥ 3	6.76	3.16–14.48	< .0001	7.36	3.09–17.56	< .0001
mFI-5 ≥ 2	5.19	2.55—10.52	< .0001	6.17	2.69–14.14	< .0001
Discharge to higher care level						
HFRS ≥ 5	6.94	2.6–18.02	< .0001	4.53	1.54–13.27	.006
mFI-11 ≥ 1	8.94	1.17–68.44	.035	5.12	.58–44.99	n.s
mFI-11 ≥ 3	4.92	1.93–12.55	.001	4.46	1.5–13.21	.007
mFI-5 ≥ 2	4.67	1.83–11.93	.001	4.56	1.56–13.28	.006
Prolonged LOS						
HFRS ≥ 5	8.92	3.23–24.12	< .0001	4.39	1.36–14.22	.014
mFI-11 ≥ 1	1.56	.49–4.9	n.s	–	–	–
mFI-11 ≥ 3	6.02	6.02–2.32	< .0001	6.01	1.46–24.74	.013
mFI-5 ≥ 2	3.91	1.52–10.04	.005	2.05	.62–6.86	n.s

CI confidence interval, *CD* Clavien/Dindo classifications of complications, *ICU* intensive care unit, *HRFS* Hospital Frailty Risk Score, *mFI* modified Frailty Index, *OR* odds ratio, *prolonged LOS* median length of stay + 1 standard deviation, *n.s.* not significant

and insurance status. No regression analysis was possible for the outcome parameter mortality due to the low number of deceased patients ($n = 5$). The results of the univariate and multivariate regression analysis for outcome variables related to frailty assessments are shown in Table 2. There was no association between the patient´s type of insurance for any of the tests, nor was insurance correlated with differences in the examined outcome parameters.

For the abovementioned assessments and outcome parameters, ROC analyses were performed in which changes in the LOS were analyzed dichotomously (prolonged LOS vs. non-prolonged LOS). The median LOS + 1 standard deviation (SD) was defined as a prolonged LOS (Fig. 1). The ROC analysis showed that the sensitivity and specificity of the three assessments did not differ in a relevant manner, and the same applies to the *area under the curve* (AUC) values as a measure of test quality.

Discussion

It has been demonstrated that frailty is a critical factor in outcomes of medical treatments. Frailty can be objectively evaluated with assessments, of which multiple types with different focuses are available. In surgery, the evaluation of frailty is primarily used for preoperative optimization of frail patients. Usually, preoperative optimization is infeasible in emergency surgery, but peri- and postoperative therapy can be optimized. Of the more than 70 validated frailty assessments, approximately 30 are available for surgical patients but very few them are feasible in emergency situations [21]. Even the *Emergency General Surgery Specific Frailty Index* (EGSFI) requires the active cooperation of the patient, which is not always possible in patients with severe acute appendicitis [29].

Thus, two well-established assessments were selected for this study: (1) the mFI and (2) the HFRS. Both can be conducted based on information and findings routinely available in the emergency room. It was shown that assessments based

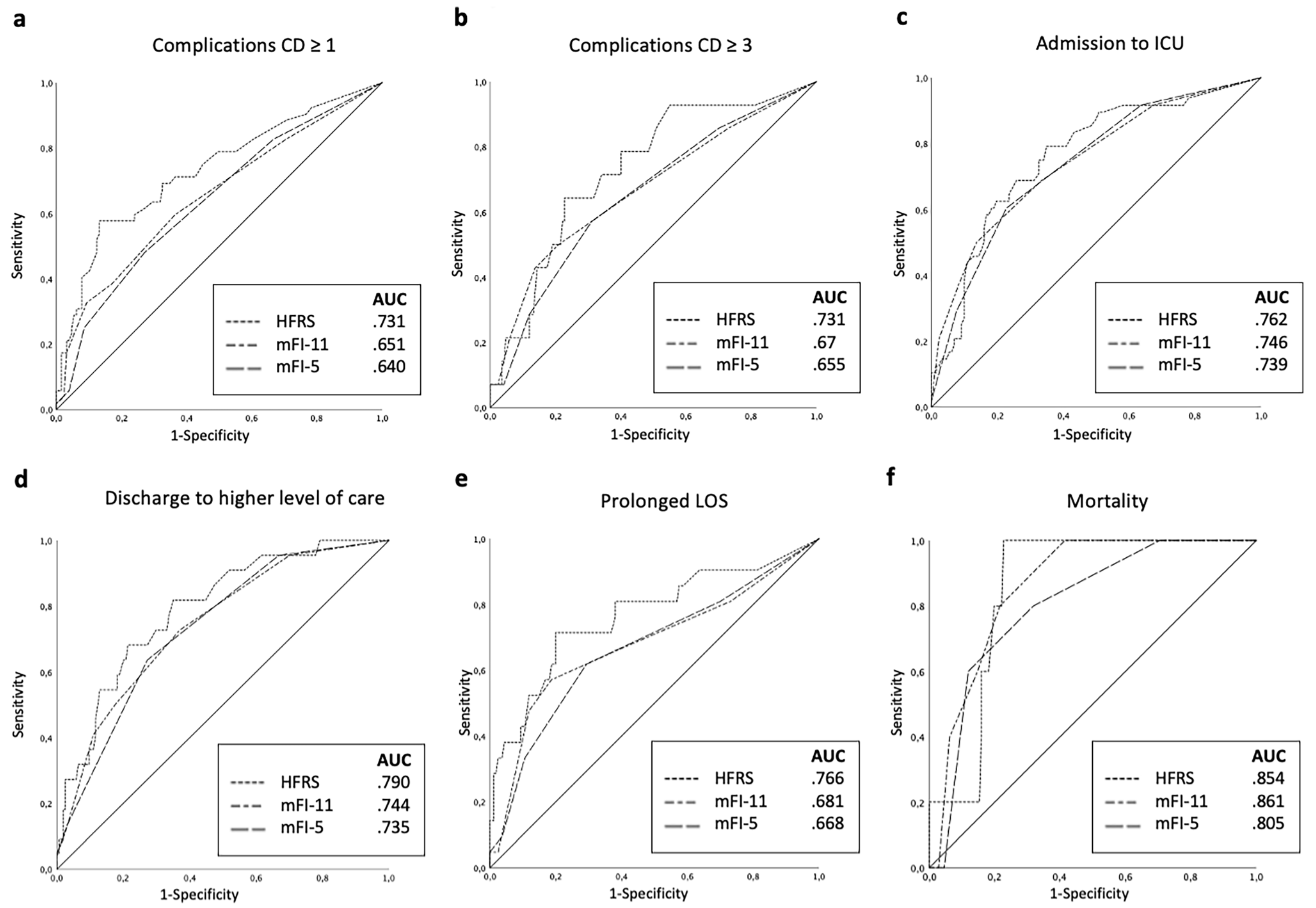

Fig. 1 Receiver operator curves (ROC) of Hospital Frailty Risk Score (HFRS) and modified Frailty Index (mFI) 5 and 11 for complications according to Clavien/Dindo classification (CD) ≥ I; **b** CD ≥ III; **c** admission to intensive care unit (ICU); **d** patient's discharge to a facility with a higher level of care than used before admission; **e** prolonged length of stay (LOS) = mean LOS + 1 standard deviation; **f** mortality

on electronic patient records recognize and determine frailty just as well as bedside assessments [30].

The choice of assessments was to some extent arbitrary, but the results of the study confirm that useful choices were made. It was possible to prove the functionality of the two assessments and compare them to a certain extent, both of which could be carried out with limited effort post hoc by non-geriatric specialized physicians. Furthermore, we demonstrated that the shorter assessment, the mFI, delivers high-quality and accurate results and is clearly correlated with the most important outcome variables. This is interesting because compared to the HFRS, the mFI delivers significantly better test quality (high accuracy of diagnosis-transfer 96.7% vs. 17.1%, $p < 0.0001$) in less time (mean 21.6 s range 0–45 s vs. 80.3 s, range 0–220 s; $p < 0.0001$). It is known that the mFI-11 and mFI-5 are equally effective in predicting frailty, although the mFI-5 is one of the easiest and fastest frailty assessments available [25].

Studies on frailty in the context of emergency surgery can mainly be categorized into two groups. First, several studies analyze data from databases, e.g., the *American College of Surgeons National Surgical Quality Improvement Project* (NISQIP). Second, there are observational clinical studies [14, 15, 18, 31–33]. The latter included patient numbers comparable to our study, while the database analyses naturally used the data of tens of thousands of patients. As previously mentioned, there are no studies with a distinct focus on appendicitis. In contrast to database queries, our study allows the assignment of the ascertained assessment to an individual clinical course. We could record additional parameters and facilitate a follow-up of 90 days, both of which are clear advantages over a database query. Moreover, a database comparable to the NISQIP is not available for Germany.

Our study demonstrates the unambiguous association between frailty and negative outcomes in elderly patients after appendectomy.

In patients with a score indicating frailty (HRFS ≥ 5 or mFI-11 ≥ 3), complications of any severity were more than twice as frequent compared with patients without signs of frailty (48.8% vs. 22.9%, $p = 0.003$), and the OR was 5.9 for a HFRS ≥ 5 (95% CI 2.7–12.8, $p < 0.0001$) and 2.9 for an mFI-11 ≥ 3 (95% CI 1.3–6.3, $p = 0.009$). For serious complications (CD ≥ III), we observed a more than threefold increase in the complication rate (17.1% vs. 5%, $p = 0.018$) and ORs of 4.9 (HFRS 95% CI 1.5–16.7, $p = 0.011$) or 3.6 (mFI-11 95% CI 1.1–11.5, $p = 0.029$). The length of inpatient stay was almost doubled in patients in whom the HFRS or mFI indicated frailty (no frailty: mean 6.6 days; HFRS ≥ 5 and mFI-11 ≥ 3 mean 12.7 days $p < 0.005$), and the OR for a prolonged LOS was 4.4 (HFRS ≥ 5; 95% CI 1.4–14.2, $p = 0.014$) resp. 6.0 (mFI-11 ≥ 3; 95% CI 1.5—24.7, $p = 0.013$). These observations are well in line with data published by other authors on frailty in emergency general surgery [14, 15, 18].

Elderly patients with elevated frailty scores were admitted significantly more often to the ICU, and this observation aligns with other studies focused on emergency surgery [18]. In our cohort, patients with an mFI ≥ 3 were 5.5 times more often admitted to the ICU (mFI-11: OR 7.4, 95% CI 3.1–17.6, $p < 0.0001$; mFI-5: OR 6.2, 95% CI 2.7–14.1, $p < 0.0001$; HFRS ≥ 5: OR 5.2, 95% CI 2.3–11.5, $p < 0.0001$) than those without evidence of frailty in the assessments (Table 2). This observation is quite interesting given that appendicitis only very rarely leads to ICU-therapy in the general population.

Our ROC analyses proved the sensitivity and specificity of the assessments for the most important outcome parameters. We were able to show that the observed relationships between frailty and negative outcome can be observed not only in dichotomous utilization of the assessments with the respective cutoffs but also across the entire range of points in the tests. The AUC, a measure of test quality, was very similar between the assessments, which is very interesting in light of the considerably higher effort required to conduct the HFRS compared to the mFI-5.

We demonstrated that frailty after appendectomy is also correlated with an increased rate of discharge to an environment with a higher care level compared to before admission (HRFS ≥ 5: OR 4.5, 95% CI 1.5–13.3, $p = 0.006$; mFI-11 ≥ 3: OR 4.5, 95% CI 1.5–13.2, $p = 0.007$; mFI-5 ≥ 2 OR 4.6, 95% CI 1.6–13.3, $p = 0.006$). This finding fits well with data published by Murphy et al. who demonstrated a reduced rate of home discharges for patients with intermediate and high frailty scores [15]. We deliberately did not choose the criteria “discharge home” or “institutional” vs. “non-institutional discharge”, as some of the patients referred for appendectomy were already residing in care facilities or retirement homes. This result demonstrates an immediate and productive application of the assessments. The modalities of a future discharge of patients with appendicitis who show frailty should be discussed and planned early in the inpatient stay such as by involving the social service.

We could observe an increase readmission rates, solely for surgical problems and only in patients with an mFI-5 ≥ 2. Rothenberg et al. showed that frailty is a risk factor for readmission but they did not study emergency surgery patients. Interestingly, frailty leads to a doubling of the readmission rate in his study, which is very similar to our observation in the subgroup with an mFI-5 ≥ 2 [34].

One objective of conducting frailty assessment in surgery is to positively influence the patient´s outcome by improving her or his preoperative condition [35]. This is hardly feasible in the context of an urgent appendectomy, and “prehabilitation” is not possible in these patients. However, even in this context, there still exist some options. For example, it is known that frailty increases the risk of postoperative delirium, which in turn is associated with consequences such as extended stay in intensive care. This risk can be countered by appropriate anesthesia (e.g., avoiding benzodiazepines, controlled depth of anesthesia). Malnutrition is another risk factor correlated with frailty and poor surgical outcomes. Frail patients can be treated early with a protein-rich, supportive diet and nutrition counseling [36].

Moreover, as we demonstrated, patients who show signs of frailty are subject to increased complications. This can be countered with greater awareness and additional examinations, such as laboratory controls or sonographies, in the postoperative course. Physiotherapy, intensified remobilization, or respiratory therapy are further options that may reduce the risk of complications in frail patients.

Important information is also provided for resource planning, such as bed occupancy or intensive care capacity. Ultimately, a demonstrated connection between frailty and increased mortality has an important implication. For example, if an older patient with frailty is informed about a necessary operation for acute appendicitis, then perioperative mortality, which reaches up to 17% (mFI-11 ≥ 3) in our data, can be emphasized differently compared to a patient without frailty. If simple tests such as the mFI can quickly and accurately detect frailty in a patient, then this can also be an opportunity for a detailed geriatric assessment which can help identify specific risk factors that can then be addressed with targeted treatment [37].

To our knowledge, this study is the first to focus on frailty in elderly patients undergoing emergency appendectomy, but a number of papers have been published that address frailty as a risk factor after emergency general surgery. This supports the stability of our observations as the results are almost entirely coherent to previously published data.

Frailty as a multifactorial clinical syndrome is not caused solely by the summation of disabilities and comorbidities. Furthermore, while there is no defined minimum age for frailty, it is well established that frailty is a syndrome of the elderly [38]. The age threshold of 65 years designating elderly patients is also widely accepted [39, 40]. The mFI has been validated for people ages 65 years old and above. While the HFRS was developed using data from patients over 75 years old, it has been successfully used in patients aged 65 years and above [41]. Our analysis shows that HFRS tends to predict worse outcomes for both over 65- and over 75-year-old patients with frailty. In this regard, our work is highlighted by the fact that we only examined frailty in patients over the age of 65 at the time of the operation. Only a small fraction of study groups investigating frailty in surgical patients undergoes this restriction [31, 42]. If other authors examine frailty across the entire age spectrum, including young people, and analyze age as a covariate, then we consider this questionable.

As mentioned at the beginning, the two most widespread concepts frame frailty as the result of the accumulation of deficits or the reduction of capacities and resources. While the underlying biological processes are largely not understood, there are established associations between frailty, immune system alterations, and inflammation. Some studies use the term “inflamm-aging”. We see increased white blood cells, CRP, TNF-α, and IL-6 in people with frailty, but it is still debated whether these are the cause or consequence of frailty [43, 44]. In the context of our study, an analysis of these parameters does not seem meaningful since acute inflammation, such as that in acute appendicitis, necessarily leads to an increase in inflammatory biomarkers. Values independent of acute inflammation are not available for our cohort.

Our study is not without limitations

First, our study is a retrospective analysis. However, since all the requested parameters were entered into the electronic patient records immediately during the treatment process and could not be modified, the risk of bias is minimal. It can be assumed that the results presented will be confirmed or even clearer if the assessments are made in real time while a patient is being admitted.

All assessments that use encoded disease data are prone to quality deficits in coding. However, since these coded data are crucial for revenues in the German health system, all employees in surgical clinics are very well trained in coding. Furthermore, at all participating centers, specialized accounting employees verify coding at dismission. Thus, it can be assumed that coding quality is very high, which minimizes potential bias.

The tests used focused on recording deficits and diseases. This leads to an overestimation of multimorbidity while motor, cognitive, social, and psychological factors are underestimated. As already mentioned, the latter factors can hardly be validly recorded in acutely ill patients and within the constraints of the emergency room.

The number of patients included is small compared to registry-based studies but is within the scope of the examined patients in comparable clinical analyses and the proportion of patients over 65 years is even slightly higher compared to that of epidemiological studies [2]. The data were collected from three independent hospitals and are very coherent with regard to all parameters. The statistical analyses were unambiguous in their statements. Only the low total number of deaths in the study population precluded the feasibility of a regression analysis of this parameter that would result in meaningful results.

The fact that old age is correlated with poor prognosis and outcomes in acute appendicitis is well documented in the literature and is hardly controversial. However, we were able to show for the first time in a clinical study that it is more so frailty, rather than age which causes poor outcomes.

Conclusion

Frailty is an important risk factor for elderly patients with acute appendicitis. While this disease is associated with low morbidity and very low mortality in younger patients, in older, frail patients, we observe an outcome that is significantly worse than would be expected based on age or comorbidities alone. In this cohort, frailty can be reliably recorded using simple assessments based on data routinely collected by each surgeon during an emergency admission. Identifying vulnerable patients is fundamental for determining targeted countermeasures and for optimizing resource planning. The latter is crucial, as the importance of understanding and treating appendicitis in the elderly population is becoming increasingly evident.

Author contributions AR—study conception and design, acquisition of data, analysis and interpretation of data, and drafting of manuscript. MR—acquisition of data and critical revision of manuscript. CCOM—acquisition of data and critical revision of manuscript. WP—acquisition of data and critical revision of manuscript. FU—acquisition of data and critical revision of manuscript. JL—study conception and design, acquisition of data, analysis and interpretation of data, and critical revision of manuscript.

Funding Open Access funding enabled and organized by Projekt DEAL. No further funding or sponsoring.

Availability of data and material Not applicable.

Code availability Not applicable.

Declarations

Conflict of interest Alexander Reinisch declares that he has no conflict of interests. Martin Reichert declares that he has no conflict of interests. Christian Charles Ondo Meva declares that he has no conflict of interests. Winfried Padberg declares that he has no conflict of interests. Frank Ulrich declares that he has no conflict of interests. Juliane Liese declares that she has no conflict of interests.

Ethics approval The study was approved by the Ethics Committee of the Justus-Liebig-University Giessen (AZ 222/20).

References

1. Ilves I, Paajanen HE, Herzig KH, Fagerström A, Miettinen PJ. Changing incidence of acute appendicitis and nonspecific abdominal pain between 1987 and 2007 in Finland. World J Surg. 2011;35(4):731–8. https://doi.org/10.1007/s00268-011-0988-8.
2. Ceresoli M, Zucchi A, Allievi N, Harbi A, Pisano M, Montori G, et al. Acute appendicitis: epidemiology, treatment and outcomes-analysis of 16544 consecutive cases. World J Gastrointest Surg. 2016;8(10):693–9. https://doi.org/10.4240/wjgs.v8.i10.693.
3. Bundesamt S: Bevölkerungspyramide. https://service.destatis.de/bevoelkerungspyramide/index.html (2020). Accessed 4.11.2020 2020.
4. Segev L, Keidar A, Schrier I, Rayman S, Wasserberg N, Sadot E. Acute appendicitis in the elderly in the twenty-first century. J Gastrointest Surg. 2015;19(4):730–5. https://doi.org/10.1007/s11605-014-2716-9.
5. Pereira B, Mendes CA, Ruano RM, Neves I, Curado RL, Oliveira R, et al. Acute appendicitis may no longer be a predominant disease of the young population. Anaesthesiol Intensive Ther. 2019;51(4):283–8. https://doi.org/10.5114/ait.2019.87332.
6. Körner H, Söndenaa K, Söreide JA, Andersen E, Nysted A, Lende TH, et al. Incidence of acute nonperforated and perforated appendicitis: age-specific and sex-specific analysis. World J Surg. 1997;21(3):313–7. https://doi.org/10.1007/s002689900235.
7. Kraemer M, Franke C, Ohmann C, Yang Q, Group AAPS. Acute appendicitis in late adulthood: incidence, presentation, and outcome. Results of a prospective multicenter acute abdominal pain study and a review of the literature. Langenbecks Arch Surg. 2000;385(7):470–81. https://doi.org/10.1007/s004230000165.
8. Kotaluoto S, Ukkonen M, Pauniaho SL, Helminen M, Sand J, Rantanen T. Mortality related to appendectomy; a population based analysis over two decades in Finland. World J Surg. 2017;41(1):64–9. https://doi.org/10.1007/s00268-016-3688-6.
9. Fugazzola P, Ceresoli M, Agnoletti V, Agresta F, Amato B, Carcoforo P, et al. The SIFIPAC/WSES/SICG/SIMEU guidelines for diagnosis and treatment of acute appendicitis in the elderly (2019 edition). World J Emerg Surg. 2020;15(1):19. https://doi.org/10.1186/s13017-020-00298-0.
10. Hubbard RE, Peel NM, Samanta M, Gray LC, Mitnitski A, Rockwood K. Frailty status at admission to hospital predicts multiple adverse outcomes. Age Ageing. 2017;46(5):801–6. https://doi.org/10.1093/ageing/afx081.
11. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet. 2013;381(9868):752–62. https://doi.org/10.1016/S0140-6736(12)62167-9.
12. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146–56. https://doi.org/10.1093/gerona/56.3.m146.
13. Watt J, Tricco AC, Talbot-Hamon C, Pham B, Rios P, Grudniewicz A, et al. Identifying older adults at risk of harm following elective surgery: a systematic review and meta-analysis. BMC Med. 2018;16(1):2. https://doi.org/10.1186/s12916-017-0986-2.
14. Fagenson AM, Powers BD, Zorbas KA, Karhadkar S, Karachristos A, Di Carlo A, et al. Frailty predicts morbidity and mortality after laparoscopic cholecystectomy for acute cholecystitis: an ACS-NSQIP cohort analysis. J Gastrointest Surg. 2020. https://doi.org/10.1007/s11605-020-04570-1.
15. Murphy PB, Savage SA, Zarzaur BL. Impact of patient frailty on morbidity and mortality after common emergency general surgery operations. J Surg Res. 2020;247:95–102. https://doi.org/10.1016/j.jss.2019.10.038.
16. Goeteyn J, Evans LA, De Cleyn S, Fauconnier S, Damen C, Hewitt J, et al. Frailty as a predictor of mortality in the elderly emergency general surgery patient. Acta Chir Belg. 2017;117(6):370–5. https://doi.org/10.1080/00015458.2017.1337339.
17. Tan HL, Chia STX, Nadkarni NV, Ang SY, Seow DCC, Wong TH. Frailty and functional decline after emergency abdominal surgery in the elderly: a prospective cohort study. World J Emerg Surg. 2019;14:62. https://doi.org/10.1186/s13017-019-0280-z.
18. Joseph B, Zangbar B, Pandit V, Fain M, Mohler MJ, Kulvatunyou N, et al. Emergency general surgery in the elderly: too old or too frail? J Am Coll Surg. 2016;222(5):805–13. https://doi.org/10.1016/j.jamcollsurg.2016.01.063.
19. Sánchez Arteaga A, Tinoco González J, Tallón Aguilar L, Anguiano Díaz G, Jiménez-Rodriguez RM, Rovira Liarde A, et al. Long-term influence of frailty in elderly patients after surgical emergencies. Eur J Trauma Emerg Surg. 2021. https://doi.org/10.1007/s00068-021-01818-6.
20. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ. 2005;173(5):489–95. https://doi.org/10.1503/cmaj.050051.
21. McDonald VS, Thompson KA, Lewis PR, Sise CB, Sise MJ, Shackford SR. Frailty in trauma: a systematic review of the surgical literature for clinical assessment tools. J Trauma Acute Care Surg. 2016;80(5):824–34. https://doi.org/10.1097/TA.0000000000000981.
22. Dapp U, Anders J, Golgert S, von Renteln-Kruse W, Minder CE. Resources and risks in old age: the LUCAS-I marker set for a classification of elderly people as fit, pre-frail and frail. First results on validity from the Longitudinal Urban Cohort Ageing Study (LUCAS), Hamburg. Z Gerontol Geriatr. 2012;45(4):262–70. https://doi.org/10.1007/s00391-012-0311-9.
23. Rolfson DB, Majumdar SR, Tsuyuki RT, Tahir A, Rockwood K. Validity and reliability of the Edmonton Frail Scale. Age Ageing. 2006;35(5):526–9. https://doi.org/10.1093/ageing/afl041.
24. Velanovich V, Antoine H, Swartz A, Peters D, Rubinfeld I. Accumulating deficits model of frailty and postoperative mortality and morbidity: its application to a national database. J Surg Res. 2013;183(1):104–10. https://doi.org/10.1016/j.jss.2013.01.021.

25. Subramaniam S, Aalberg JJ, Soriano RP, Divino CM. New 5-factor modified frailty index using American college of surgeons NSQIP data. J Am Coll Surg. 2018;226(2):173-81.e8. https://doi.org/10.1016/j.jamcollsurg.2017.11.005.
26. Gilbert T, Neuburger J, Kraindler J, Keeble E, Smith P, Ariti C, et al. Development and validation of a Hospital Frailty Risk Score focusing on older people in acute care settings using electronic hospital records: an observational study. Lancet. 2018;391(10132):1775–82. https://doi.org/10.1016/S0140-6736(18)30668-8.
27. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205–13. https://doi.org/10.1097/01.sla.0000133083.54934.ae.
28. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–83.
29. Engelhardt KE, Reuter Q, Liu J, Bean JF, Barnum J, Shapiro MB, et al. Frailty screening and a frailty pathway decrease length of stay, loss of independence, and 30 day readmission rates in frail geriatric trauma and emergency general surgery patients. J Trauma Acute Care Surg. 2018;85(1):167–73. https://doi.org/10.1097/TA.0000000000001931.
30. Weiss HK, Stocker BW, Weingarten N, Engelhardt KE, Cook BA, Posluszny JA. Electronic medical record versus bedside assessment: how to evaluate frailty in trauma and emergency general surgery patients? J Surg Res. 2020;246:464–75. https://doi.org/10.1016/j.jss.2019.09.014.
31. McIsaac DI, Moloo H, Bryson GL, van Walraven C. The Association of frailty with outcomes and resource use after emergency general surgery: a population-based cohort study. Anesth Analg. 2017;124(5):1653–61. https://doi.org/10.1213/ANE.0000000000001960.
32. Kenig J, Mastalerz K, Lukasiewicz K, Mitus-Kenig M, Skorus U. The Surgical Apgar Score predicts outcomes of emergency abdominal surgeries both in fit and frail older patients. Arch Gerontol Geriatr. 2018;76:54–9. https://doi.org/10.1016/j.archger.2018.02.001.
33. Khan M, Jehan F, Zeeshan M, Kulvatunyou N, Fain MJ, Saljuqi AT, et al. Failure to rescue after emergency general surgery in geriatric patients: does frailty matter? J Surg Res. 2019;233:397–402. https://doi.org/10.1016/j.jss.2018.08.033.
34. Rothenberg KA, Stern JR, George EL, Trickey AW, Morris AM, Hall DE, et al. Association of frailty and postoperative complications with unplanned readmissions after elective outpatient surgery. JAMA Netw Open. 2019;2(5): e194330. https://doi.org/10.1001/jamanetworkopen.2019.4330.
35. Shah R, Attwood K, Arya S, Hall DE, Johanning JM, Gabriel E, et al. Association of frailty with failure to rescue after low-risk and high-risk inpatient surgery. JAMA Surg. 2018;153(5): e180214. https://doi.org/10.1001/jamasurg.2018.0214.
36. Mende A, Riegel AK, Plümer L, Olotu C, Goetz AE, Kiefmann R. Determinants of perioperative outcome in frail older patients. Dtsch Arztebl Int. 2019;116(5):73–82. https://doi.org/10.3238/arztebl.2019.0073.
37. Benzinger P, Eidam A, Bauer JM. Clinical importance of the detection of frailty. Z Gerontol Geriatr. 2021;54(3):285–96. https://doi.org/10.1007/s00391-021-01873-z.
38. Rodríguez-Mañas L, Féart C, Mann G, Viña J, Chatterji S, Chodzko-Zajko W, et al. Searching for an operational definition of frailty: a Delphi method based consensus statement: the frailty operative definition-consensus conference project. J Gerontol A Biol Sci Med Sci. 2013;68(1):62–7. https://doi.org/10.1093/gerona/gls119.
39. Orimo H, Ito H, Suzuki T, Araki A, Hosoi T, Sawabe M. Reviewing the definition of "elderly." Geriatr Gerontol Int. 2006;6:149–58. https://doi.org/10.1111/j.1447-0594.2006.00341.x
40. OECD (2022) Elderly population (indicator). https://doi.org/10.1787/8d805ea1-en
41. Kundi H, Çetin EHÖ, Canpolat U, Aras S, Celik O, Ata N, et al. The role of frailty on adverse outcomes among older patients with COVID-19. J Infect. 2020;81(6):944–51. https://doi.org/10.1016/j.jinf.2020.09.029.
42. McIsaac DI, Taljaard M, Bryson GL, Beaulé PE, Gagné S, Hamilton G, et al. Frailty as a predictor of death or new disability after surgery: a prospective cohort study. Ann Surg. 2020;271(2):283–9. https://doi.org/10.1097/SLA.0000000000002967.
43. Soysal P, Stubbs B, Lucato P, Luchini C, Solmi M, Peluso R, et al. Inflammation and frailty in the elderly: a systematic review and meta-analysis. Ageing Res Rev. 2016;31:1–8. https://doi.org/10.1016/j.arr.2016.08.006.
44. Alberro A, Iribarren-Lopez A, Sáenz-Cuesta M, Matheu A, Vergara I, Otaegui D. Inflammaging markers characteristic of advanced age show similar levels with frailty and dependency. Sci Rep. 2021;11(1):4358. https://doi.org/10.1038/s41598-021-83991-7.

6. Erklärung

Ich erkläre hiermit, dass die vorliegende kumulative Habilitationsschrift „Untersuchungen zu aktuellen pathomechanistischen und therapeutischen Aspekten der akuten Appendizitis“ eigenständig und ohne fremde Hilfe von mir verfasst wurde. Ich erkläre hiermit, keine anderen als die angegebenen Quellen verwandt zu haben, wobei wörtlich oder annähernd wörtlich aus anderen Arbeiten entnommene Stellen als solche genau erkenntlich gemacht worden sind.

Dr. med. Alexander Reinisch-Liese